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No. ——

Supreme Court, U.S.
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IN THE

Supreme Court of the United States

OCTOBER TERM, 1989

SANDOZ PHARMACEUTICALS CORPORATION,
AND 14 BOXES, MORE OR LESS, . . .
FIORINAL WITH CODEINE NO. 3,
Petitioner,

v.

UNITED STATES OF AMERICA,
Respondent.

PETITION FOR WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE SIXTH CIRCUIT

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QUESTION PRESENTED FOR REVIEW

Whether the U.S. Court of Appeals for the Sixth Circuit erred in affirming a summary judgment determination in which the doctrine of offensive collateral estoppel was applied to preclude Petitioner from litigating the issue of whether Fiorinal with Codeine No. 3 is a "new drug" under 21 U.S.C. § 321(p). The decision having collateral estoppel effect was a summary judgment determination in another circuit that two similar but different drugs were "new drugs."

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UNITED STATES OF AMERICA,
Respondent.

PETITION FOR WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE SIXTH CIRCUIT

The petitioner, Sandoz Pharmaceuticals Corporation ("Sandoz")[1], respectfully prays that a writ of certiorari issue to review the judgment of the U.S. Court of Appeals for the Sixth Circuit entered in this proceeding on January 25, 1990.

OPINIONS BELOW

The decision of the U.S. Court of Appeals for the Sixth Circuit, *United States v. Sandoz Pharmaceuticals Corp.*, 894 F.2d 825 (6th Cir. 1990), appears as Appendix A. Appendix ("App."), 1a. This decision affirmed the judg-

[1] The parent company of Sandoz Pharmaceuticals Corporation is Sandoz Corporation; it has no subsidiaries.

ment of the U.S. District Court for the Southern District of Ohio ("District Court"), *United States v. An Article of Drug . . . Fiorinal with Codeine No. 3*, No. C-2-86-741 (S.D.Ohio, May 24, 1988) (judgment entered on June 22, 1988), which appears as Appendix B. App., 9a. The District Court made a finding of collateral estoppel based on the decision of the U.S. District Court for the District of New Jersey ("N.J. Court"), *United States v. 225 Cartons . . . Fiorinal with Codeine No. 1 and Fiorinal with Codeine No. 2*, 687 F. Supp. 946 (D.N.J. 1988), *aff'd*, 871 F.2d 409 (3rd Cir. 1989), which appears as Appendix C. App., 22a.

JURISDICTION

The judgment of the Court of Appeals was entered on January 25, 1990. This petition was filed within 90 days of the judgment entry, pursuant to 28 U.S.C. § 2101(c) and Rule 13.1 of the Rules of the Supreme Court of the United States. This Court's jurisdiction is invoked under 28 U.S.C. § 1254(1).

STATUTES INVOLVED

The pertinent statutory and regulatory provisions are 21 U.S.C. §§ 321(p), 355(a) and 355(d), and 21 C.F.R. § 300.50 (1989); these are set out as Appendices D, E, F, and G.

STATEMENT OF THE CASE

This case arises under the Federal Food, Drug, and Cosmetic Act ("the Act"), 21 U.S.C. § 301 et seq. It is an *in rem* seizure action under 21 U.S.C. § 334. Respondent United States of America ("the government") seized a quantity of the combination prescription drug product Fiorinal with Codeine No. 3 ("FWC No. 3"), alleging that it is a "new drug" under 21 U.S.C. § 321(p) that therefore cannot be shipped in interstate commerce under 21 U.S.C. § 355(a). Sandoz is the manufacturer of FWC No. 3 and the claimant in the case.

Under the Act, a "new drug" cannot be shipped in interstate commerce unless it is the subject of a New Drug Application ("NDA") that has been approved by the Food and Drug Administration ("FDA"). 21 U.S.C. § 355(a). The Act provides that a drug is not a "new drug" requiring premarket approval if it is generally recognized among qualified experts as safe and effective for its intended use. 21 U.S.C. § 321(p). The Act does not define "general recognition," but this Court addressed the question of what standard of evidence should be required as a basis for "general recognition" in two companion cases, *Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 93 S.Ct. 2469, 37 L.Ed.2d 207 (1973) and *Weinberger v. Bentex Pharmaceuticals, Inc.*, 412 U.S. 645, 93 S.Ct. 2488, 37 L.Ed.2d 235 (1973). In *Hynson*, this Court stated that

> . . . the hurdle of "general recognition" of effectiveness requires at least "substantial evidence" of effectiveness for approval of an NDA.

Id., 412 U.S. at 629, 93 S.Ct. at 2483. The "substantial evidence" that the Court was referring to is the same kind of evidence of effectiveness that FDA is required to find in order to approve an NDA. "Substantial evidence" is defined in the Act as:

> . . . evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

21 U.S.C. § 355(d). In *Bentex*, the Court modified its statement in *Hynson* by acknowledging that it would be appropriate to except some drugs from the requirement

that "general recognition" of effectiveness be based on "substantial evidence." It stated:

> It may, of course, be true that in some cases general recognition that a drug is efficacious might be made without the kind of scientific support necessary to obtain approval of an NDA.

Bentex, 412 U.S. at 652, 93 S.Ct. at 2493.

The question of whether particular studies constitute "substantial evidence" of effectiveness depends on whether experts could "fairly and responsibly" base their conclusions on them. The legislative history of the Drug Amendments of 1962, Pub.L. 87-781, 76 Stat. 780 (October 10, 1962), which added the concept of substantial evidence of effectiveness to the Act, indicates that Congress recognized that there would be differences of opinion as to the conclusions to be reached based on particular clinical studies. This legislative history suggests that agreement by less than all, or even less than a majority, of experts as to the results of studies that show efficacy is sufficient to cause those studies to constitute "substantial evidence." *See* S. Rep. No. 1744 (Part 1), 87th Cong., 2d Sess. 16 (1962); *reprinted in* 1962 U.S. Code Cong. & Ad. News 2892 (permitting expert opinion to be based on adequate tests even when there is preponderant evidence to the contrary); S. Rep. No. 1744 (Part 2), 87th Cong., 2d Sess. 6 (1962) (distinguishing between "preponderant evidence" and "substantial evidence"). FDA has further modified the concept of "substantial evidence" for combination drugs. Under the agency's policy, "[t]wo or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects . . . ." 21 C.F.R. § 300.50(a) (1989). Since FWC No. 3 is a combination product, the issue of its "general recognition" includes the issue of whether each ingredient contributes to the product's claimed effect.

FWC No. 3 has been marketed by Sandoz since 1963. Since that time, FDA has never questioned the product's safety. In this proceeding. the government does not dispute the product's *actual* effectiveness, but only whether the product is "generally recognized" as effective. Since its introduction, FWC No. 3 has been marketed in good faith on the basis that it is not a "new drug" under the Act. Prior to marketing, Sandoz requested FDA's opinion as to whether the product was a "new drug" that would require the filing of an NDA. In a letter of August 6, 1962, FDA stated that FWC No. 3 was not a "new drug." [2]

In addition to FWC No. 3, Sandoz has also marketed two related but distinctly different drugs, Fiorinal with Codeine No. 1 and Fiorinal with Codeine No. 2.[3] FWC No. 3 contains 30 milligrams ("mg") codeine phosphate (a narcotic analgesic), which is twice as much as that contained in Fiorinal with Codeine No. 2 and four times as much as in Fiorinal with Codeine No. 1. FWC No. 3 (and the related products) also contain 325 mg aspirin (a non-narcotic analgesic), 50 mg butalbital (a barbituate), and 40 mg caffeine (an analgesic adjuvant).[4]

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[2] In May 1968, FDA purported to revoke all of its previously provided "not new drug" opinions. *See* 21 C.F.R. § 310.100(d) (1989). The notice of revocation specifically disclaimed any implication that all affected products were, as a result, "new drugs." It simply asserted that each product was now subject to reevaluation on a case-by-case basis. There is, then, no question that FWC No. 3 was legally marketed by Sandoz when it was first introduced.

[3] Sandoz ceased marketing Fiorinal with Codeine No. 1 and Fiorinal with Codeine No. 2 in 1988.

[4] Prior to 1983, FWC No. 3 contained phenacetin as one analgesic ingredient. This ingredient was removed in 1983 pursuant to an FDA directive pertaining to all phenacetin-containing products. *See* 47 Fed. Reg. 34636 (August 10, 1982). In accordance with this directive, additional aspirin was substituted for phenacetin on a milligram-for-milligram basis. In general, no additional studies demonstrating the safety and effectiveness of the reformulated products were required by FDA. *Id.* at 34641.

FWC No. 3 is an analgesic product indicated for all types of acute pain and discomfort that are less serious than those requiring morphine. It is particularly useful for patients who have developed a cycle of pain and anxiety such as occurs with tension headache. FWC No. 3 has consistently been the largest-selling prescription drug in the country for this indication. (The related products, Fiorinal with Codeine No. 1 and Fiorinal with Codeine No. 2, have been comparatively minor, accounting for less than one-tenth the sales of FWC No. 3 in 1988.)

The documents submitted in this litigation raise a genuine issue of material fact as to whether FWC No. 3 is generally recognized as effective. The government supported its Motion for Summary Judgment with the declarations of six experts who discussed three published studies and concluded that FWC No. 3 is not generally recognized as effective. Sandoz supported its response to the government's motion by submitting six published studies (including the three used by the government) as adequate and well-controlled studies supporting the safety and effectiveness of FWC No. 3. It also submitted the declarations of eight physicians and scientists which indicated that the studies are adequate, well-controlled, and support general recognition of safety and effectiveness and the contribution of each component to the claimed effect.

Notwithstanding this sharp difference of opinion among experts, the District Court did not reach the issue of "general recognition" or any other issue on the merits. Instead, it held that Sandoz is collaterally estopped from litigating "the issue of whether [FWC] No. 3 is a new drug" based on the collateral estoppel effect of a decision of the N.J. Court that Fiorinal with Codeine No. 1 and Fiorinal with Codeine No. 2 are "new drugs." App., 17a. The following discussion outlines the chronology of events that culminated in the District Court's decision:

The government instituted this *in rem* action against a specified quantity of FWC No. 3 by filing a Complaint for Forfeiture on June 17, 1986, in the District Court. Sandoz filed a claim as the owner of the drugs, an answer, and a jury demand. Approximately four months later, on October 3, 1986, the government brought a separate *in rem* proceeding against specified quantities of Fiorinal with Codeine No. 1 and Fiorinal with Codeine No. 2 in the N.J. Court.

After filing its answer in the Ohio District Court, Sandoz assembled its evidence and formulated discovery inquiries. On February 3, 1987, it filed its first discovery request. Shortly thereafter, however, the government filed a Motion for Summary Judgment and a Motion for a Protective Order to hold discovery in abeyance. Sandoz marshalled evidence and experts' opinions in response to the Motion for Summary Judgment, and also documented the need for discovery in its Motion for Continuance to Permit Discovery to Oppose Plaintiff's Motion for Summary Judgment. At a conference held on March 19, 1987, the U.S. Magistrate denied Sandoz' Motion for Continuance to Permit Discovery and granted the government's Motion for a Protective Order, staying discovery until the court ruled on the Motion for Summary Judgment.

Meanwhile, on April 1, 1987, while Sandoz was in the process of responding to the summary judgment motion against its major product, FWC No. 3, the government filed a Motion for Summary Judgment in the N.J. Court with respect to the minor products, Fiorinal with Codeine No. 1 and Fiorinal with Codeine No. 2. Sandoz filed a Motion to Stay Proceedings pending a decision on FWC No. 3 in Ohio. At a hearing on this motion on May 11, 1987, the N.J. Court expressed the view that "[i]deally [the Ohio and New Jersey cases] should be tried in the same proceeding." Transcript of Proceedings, Civil No. 86-3877, at 6 (May 11, 1987) ("N.J. Tran-

script"). Sandoz stated its need for discovery and its agreement that the cases could be consolidated in a proceeding that fairly recognized the distinctions among the three different drugs and their supporting evidence. *Id.* at 6-8. The government, however, opposed such consolidation and expressed the view that Sandoz' evidence in the New Jersey case was "far less compelling" than its evidence supporting FWC No. 3 in Ohio. *Id.* at 10. The court recognized the differences between the drugs involved and decided that "[t]he government is entitled to proceed as best it can on developing the distinct issues relating to those two [drugs]." *Id.* It denied the stay and stated that it would simultaneously consider the government's summary judgment motion, Sandoz' response, and Sandoz' Motion for Continuance to Conduct Discovery under Fed. R. Civ. P. 56(f). *Id.* at 10-12. Sandoz filed its Response and Motion for Continuance by the end of June 1987. On March 8, 1988, the N.J. Court issued an opinion granting summary judgment for the government. It held that Fiorinal with Codeine No. 1 and Fiorinal with Codeine No. 2 are "new drugs" under 21 U.S.C. § 321(p). App., 53a. Sandoz appealed the decision.

Following the N.J. Court's decision, the government filed with the Ohio District Court a "Motion for Judgment" on March 16, 1988. This motion provided the court a copy of the New Jersey decision and requested judgment "on the grounds that the factual and legal issues have already been decided adversely to the Claimant." At the same time, the government filed a Motion to Amend its Complaint to Include Injunctive Relief. On May 24, 1988, the Ohio District Court issued its decision ruling against FWC No. 3 on the basis of collateral estoppel. App., 18a. It granted the government's motions for summary judgment and for an injunction, but stayed the enforcement of its order pending an appeal to the Sixth Circuit and an appeal of the New Jersey case to the U.S. Court of Appeals for the Third Circuit.

On March 27, 1989, the U.S. Court of Appeals for the Third Circuit affirmed the judgment of the N.J. Court. *United States v. 225 Cartons . . . Fiorinal with Codeine No. 1 and Fiorinal with Codeine No. 2*, 871 F.2d 409 (3rd Cir. 1989). On January 25, 1990, the Sixth Circuit affirmed the decision of the Ohio District Court, but stayed its mandate pending this petition for certiorari.

In addition to pursuing this litigation to resolve the status of FWC No. 3, Sandoz filed an NDA on February 1, 1985 for the approval of the product (without waiving any of its rights to the status of FWC No. 3 as being not a new drug under 21 U.S.C. § 321(p)). The NDA has been under review at FDA since that time, and Sandoz believes that approval of the NDA is imminent.

REASONS FOR ALLOWANCE OF THE WRIT

This case represents the first time that collateral estoppel has been used to determine that a drug is a "new drug" based on a finding that a different but related product is not "generally recognized" as effective. This result contradicts holdings of this Court with respect to the definition of "drug" under the Act and with respect to the correct application of the doctrine of collateral estoppel. As the following arguments will demonstrate, a drug product's "new drug" status must be resolved in a proceeding on the merits, and it is inappropriate to use collateral estoppel to subvert this requirement.

The inapplicability of collateral estoppel to "new drug" determinations is an issue squarely faced in this case with implications that go far beyond this case. The resolution of this issue will affect many manufacturers of the approximately 1,800[5] drugs that are not now covered by an NDA or an abbreviated NDA and that may be subject to FDA enforcement action. Many of these

[5] This figure was provided by FDA staff in an informal communication on April 12, 1990.

products contain similar ingredients but are distinctly different drugs, and the use of collateral estoppel against such products threatens to obscure with a legal maneuver the pharmacological differences between products that historically have been analyzed in separate proceedings on the merits.

I. A COURT MAY NOT DECIDE A CASE IN A WAY THAT CAUSES A DRUG PRODUCT TO BECOME A "NEW DRUG" IF THE COURT DOES NOT REACH THE MERITS OF THE CASE

In *United States v. Generix Drug Corp.*, 460 U.S. 453, 103 S.Ct. 1298, 75 L.Ed.2d 198 (1983), the Supreme Court held that the term "drug" means "entire drug product, complete with active and inactive ingredients," and indicated clearly that drugs which are not bioequivalent to one another are different drugs for purposes of determining whether they are "new drugs" under 21 U.S.C. § 321(p).[6] This holding finds a basis in pharmaceutical science, which recognizes that any ingredient in a combination drug product may act differently in a differently composed combination. As a scientific matter, each combination drug must be evaluated on its own merits, notwithstanding the action of its ingredients in any other combination.

This scientific basis for *Generix* indicates that, if two combination drugs are similar[7] but not identical, it may

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[6] In general, two drugs are "bioequivalent" if the rate and extent of absorption of the two drugs are not significantly different. *See* 21 U.S.C. § 355(j)(7)(B).

[7] Similarity may arise from the two drugs having some but not all active ingredients in common, or having the same active ingredients but in different proportion, or having identical active ingredients but different inactive ingredients and being demonstrably not bioequivalent. *Generix* left open the question of whether two products would be considered identical if they had identical active ingredients, different inactive ingredients, and were bioequivalent.

be possible to conclude, based on an analysis of the first drug, that the second drug is *likely* to have the same characteristics of safety and effectiveness as the first. However, because of the differences between the two drugs, it is not possible to be *certain* about the characteristics of the second product unless that product itself is analyzed.

Since "new drug" status is dependent on whether or not a drug is safe, effective, and generally recognized as such, the same analysis applies to a determination of that status. It may be possible to conclude, based on the "new drug" status of the first drug, that a second, similar drug is likely to have the same status. However, as a legal matter, "new drug" status cannot be made certain until the second drug itself is analyzed in light of the available evidence. Differences in composition between the two drugs could cause the "general recognition" of one drug to be supported by the evidence while that of the other remained unsupported. Even if the two products had identical ingredients their "new drug" status could differ if the studies conducted using one drug were more complete than those conducted using the other (and there were no studies demonstrating bioequivalence of the two drugs).

For example, FWC No. 3 contains more than twice as much codeine as the lower-strength products that were found by the N.J. Court to be "new drugs." As a result, FWC No. 3 is likely to have a more noticeable effect than the lower-strength products, and the study data which did not support a finding of general recognition for the lower-strength products might support such a finding for FWC No. 3. Moreover, the studies conducted using FWC No. 3 are considerably different from, and more complete than, those conducted using the products at issue in New Jersey. Accordingly, although the finding of the N.J. Court increases the likelihood that FWC No. 3 is a "new drug," it does not make such a conclusion certain.

Generix did not address the legal procedures under which a "new drug" determination must be made, but the conclusions that flow from the scientific basis for *Generix*, as described above, make those procedures reasonably obvious: each drug that is the subject of a "new drug" determination must be the subject of a proceeding on the merits. Such a proceeding might be in summary form, depending on the quantity and quality of evidence submitted, but at the very least it must be a proceeding that focuses on the drug at issue, not some other drug.

In fact, FDA's practice has been consistent with this view of *Generix*. For example, in the agency's Drug Efficacy Study Implementation ("DESI") notices, it has attempted to apply its conclusions regarding the effectiveness of drugs that were covered by NDAs during the period 1938-62 to all "identical, related or similar" drugs. However, the agency's regulations are careful to provide for a proceeding on the merits for each of these drugs:

> All persons with an interest in a product that is identical, related, or similar to a drug listed in a drug efficacy notice or a notice of opportunity for a hearing will be given the same opportunity as the applicant [for the drug listed in the notice] to submit data and information, to request a hearing, and to participate in any hearing.

21 C.F.R. § 310.6(a) (1989). While summary judgment remains available both to the agency and to the courts, such a summary proceeding would have to be on the merits of the drug at issue.

The Sixth Circuit's decision with respect to FWC No. 3 contravenes this Court's analysis in *Generix* of the circumstances under which two products constitute the same "drug." By affirming the use of collateral estoppel, the Sixth Circuit treats FWC No. 3 as identical with the lower-strength products that were evaluated by the N.J. Court, but under *Generix* these products are not iden-

tical. Instead, the analysis of *Generix* indicates that FWC No. 3 should be analyzed as a separate drug. Accordingly, the Sixth Circuit's decision should be reversed and the case remanded for a determination on the merits.

II. COLLATERAL ESTOPPEL IS INAPPROPRIATE FOR THE RESOLUTION OF AN ULTIMATE ISSUE IF THAT ISSUE WAS NOT RESOLVED IN A PRIOR PROCEEDING

Just as *Generix* requires that two drug products be identical before they are susceptible to being treated identically under the Federal Food, Drug, and Cosmetic Act, so the line of cases of which *Parklane Hosiery Co. Inc. v. Shore*, 439 U.S. 322, 99 S.Ct. 645, 58 L.Ed.2d 552 (1979), is an example require that the issues between two cases be identical before they are susceptible to being resolved identically under the doctrine of collateral estoppel. As the Court said in *Parklane*:

> Collateral estoppel . . . has the dual purpose of protecting litigants from the burden of relitigating an *identical* issue . . . and of promoting judicial economy by preventing needless litigation.

Parklane, 439 U.S. at 326, 99 S.Ct. at 649 (emphasis supplied). *See also Blonder-Tongue Laboratories, Inc. v. Univ. of Illinois Foundation*, 402 U.S. 313, 323, 91 S.Ct. 1434, 1440, 28 L.Ed.2d 788 (1971).

Not only must an issue be identical, it must also be "ultimate." This Court has stated that, under the doctrine of collateral estoppel,

> [t]he normal rule is that a prior judgment need be given no conclusive effect at all unless it establishes one of the ultimate facts in issue in the subsequent proceeding. So far as merely evidentiary or "mediate" facts are concerned, the doctrine of collateral estoppel is inoperative.

Yates v. United States, 354 U.S. 298, 338, 77 S.Ct. 1064, 1087, 1 L.Ed.2d 1356 (1957), *overruled on other*

grounds, Burks v. United States, 437 U.S. 1, 98 S.Ct. 2141, 57 L.Ed.2d 1 (1978), *citing The Evergreens v. Nunan*, 141 F.2d 927 (2nd Cir. 1944) *cert. denied* 323 U.S. 720 (1944). Judge Learned Hand explained the difference between "ultimate" and "mediate" facts or issues in *The Evergreens*:

> . . . [A] "fact" may be one of two kinds. It may be one of those facts, upon whose combined occurrence the law raises the duty, or the right, in question; or it may be a fact, from whose existence may be rationally inferred the existence of one of the facts upon whose combined occurrence the law raises the duty, or the right. The first kind of fact we shall for convenience call an "ultimate" fact; the second, a "mediate datum." "Ultimate" facts are those which the law makes the occasion for imposing its sanctions.

The Evergreens, 141 F.2d at 928.

The elements of collateral estoppel apply, then, to issues that are identical and ultimate. As an example of the effect of this rule, consider Drugs A and B, where the two drugs are similar but not identical and not bioequivalent. In the first proceeding, Drug A is found to be a "new drug." In the second proceeding, the ultimate issue is the "new drug" status of Drug B. Since this issue is not identical to either an ultimate or mediate issue in the first proceeding, the doctrine of collateral estoppel should not apply.

The Sixth Circuit's decision in this case would have collateral estoppel operate when the "new drug" issues (i.e., between FWC No. 3 in Ohio and Fiorinal with Codeine Nos. 1 and 2 in New Jersey) are related but not identical. App. 4a-5a. This position contravenes cases such as *Parklane* and *Yates* which require identical issues before collateral estoppel can operate. The correct result under these cases is that the issue of the "new drug" status of FWC No. 3 be addressed on the merits.

III. COLLATERAL ESTOPPEL IS INAPPROPRIATE FOR THE RESOLUTION OF AN UNMIXED QUESTION OF LAW

In both the N.J. Court and the Ohio District Court, Sandoz submitted detailed clinical studies demonstrating the safety and effectiveness of the products at issue in those courts. Each of these studies met the statutory and regulatory requirements for adequate and well-controlled studies, and each of Sandoz' experts concluded that these studies formed a rational basis for their opinion that the products at issue are generally recognized as effective. The N.J. Court, however, concluded that, because the studies did not specifically show the contribution of certain of the ingredients to the effectiveness of certain of the products at issue (even though such contribution could rationally be inferred from the data), then all of Sandoz' studies, and the opinions of all of its experts, failed.

The N.J. Court's decision in this respect turned on its adoption of the "identical-drug" rule, i.e., that studies in support of effectiveness must be conducted with the identical drug or its bioequivalent. App., 51a-53a. This rule appears nowhere in the statute or regulations; it is an FDA policy that the N.J. Court ordained as law when it stated:

> I conclude that the proper rule and the rule that will be followed in this circuit is that the combination policy of 21 C.F.R. § 300.50 can only be met by studies of the particular drug product at issue or a drug having the same active ingredients which is demonstrably its bioequivalent.

App., 51a.[8] The entire result of the New Jersey case depended on this conclusion.

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[8] The Third Circuit upheld the application of the "identical-drug" rule. *225 Cartons*, 871 F.2d at 416-418.

When the Ohio District Court held that the New Jersey decision had a collateral estoppel effect on FWC No. 3, neither that court nor the Sixth Circuit had adopted the "identical-drug" rule. The District Court did not mention the rule but adopted it tacitly. It considered this issue not under the principle of *stare decisis* (whereby it could have analyzed the merits of applying the rule to the unique factual situation of FWC No. 3), but under the principle of collateral estoppel (whereby the rule was applied as though FWC No. 3 was identical to Fiorinal with Codeine No. 1 and Fiorinal with Codeine No. 2). Thus, the District Court treated the "identical-drug" rule not as a mixed question of fact and law, but as an unmixed question of law. Just as in the N.J. Court, the entire result of the case depended on this conclusion of law.

The Supreme Court has specifically held that collateral estoppel does not apply to unmixed questions of law. In *United States v. Moser*, 266 U.S. 236, 242, 45 S.Ct. 66, 67, 69 L.Ed. 262 (1924), it stated:

> [T]he doctrine of res judicata does not apply to . . . unmixed questions of law. Where, for example, a court in deciding a case has enunciated a rule of law, the parties in a subsequent action upon a different demand are not estopped from insisting that the law is otherwise, merely because the parties are the same in both cases.

The Court has indicated that this rule applies to the "[u]nreflective invocation of collateral estoppel." *Montana v. United States*, 440 U.S. 147, 163, 99 S.Ct. 970, 978, 59 L.Ed.2d 210 (1979). *Cf., United States v. Stauffer Chemical Co.*, 464 U.S. 165, 170 n.3, 104 S. Ct. 575, 578 n.3, 78 L.Ed.2d 388 (1984) (restating the *Moser* language in the context of differences in subject matter). As the Sixth Circuit recognized, this rule provides for the relitigation of an unmixed question of law where such relitigation is warranted because of sufficient differences between successive cases. App., 5a. This rule

is particularly appropriate where, as here, the collateral estoppel would operate between two circuits, thus foreclosing the opportunity for development in other circuits of more satisfactory interpretations of complex statutory provisions. *See Divine v. Commissioner of Internal Revenue*, 500 F.2d 1041, 1048 (2d Cir. 1974) (there are "formidable policy justifications for sanctioning the . . . relitigation in different circuits of legally identical tax issues, factually differentiable only in the identity of the taxpayer involved").

The Sixth Circuit's examination of this issue did not focus on the "identical-drug" rule but instead focused on the N.J. Court's factual analysis of clinical studies. App., 5a. This misfocus suggests that somehow this factual analysis formed the basis for the N.J. Court's adoption of the "identical-drug" rule. In fact, however, that rule was not the creation of an application of facts to law, but was purely a legal creation. *See* app., 51a. Moreover, the Sixth Circuit failed to recognize that, even if the "identical-drug" rule was a mixed question of fact and law when it was devised by the N.J. Court, it was tacitly adopted by the District Court not as a fact-based rule but purely as a question of law. Further, the Sixth Circuit erroneously indicated that the differences between the Ohio and New Jersey cases are insufficient to warrant application of the unmixed-question-of-law rule when in fact, as discussed in Part II above, the ultimate issues subject to collateral estoppel between the two cases are significantly different.

Accordingly, under the principles stated in *Moser*, *Montana* and *Stauffer*, the N.J. Court's "identical-drug" rule should not have collateral estoppel effect. The case should be remanded for a determination on the merits as to whether the "identical-drug" rule is applicable to the factual situation posed by FWC No. 3.

IV. THE USE OF OFFENSIVE COLLATERAL ESTOPPEL IS INAPPROPRIATE WHEN IT IS UNFAIR TO THE DEFENDING PARTY

Parklane requires that the application of offensive collateral estoppel be fair to the defending party: for example, the party must have had sufficient incentive to defend the first action, must not have been forced to defend in an inconvenient forum, and must have been able to engage in full scale discovery. "The problem of unfairness is particularly acute in cases of offensive estoppel . . . because the defendant against whom estoppel is asserted typically will not have chosen the forum in the first action." *Parklane*, 439 U.S. at 331 n.15, 99 S. Ct. at 651 n.15.

The Sixth Circuit found that there was no unfairness to Sandoz under *Parklane*, relying in part on its conclusion that "there is nothing in the record to indicate that the evidence presented in the New Jersey action differed from the evidence presented here." App., 7a. This conclusion is erroneous, however, because of a significant difference in the evidence: the opinions of medical experts.

The resolution of the ultimate fact of general recognition of effectiveness depends on the weighing of evidence by experts in the exercise of their judgment. The scientific evidence in support of FWC No. 3 is stronger than that in support of the products at issue in New Jersey. (There are four studies on FWC No. 3, including one with the new formulation and two designed to evaluate the critical codeine ingredient. By comparison, there are only two studies on Fiorinal with Codeine No. 2 and none on Fiorinal with Codeine No. 1. App., 31a-36a.) Since FWC No. 3 is the highest strength of the three products, it could be found by experts to be effective even if the lower strength products were not. However, not only did the N.J. Court not evaluate the evidence specific to FWC No. 3, it dismissed that evidence out of hand because, under its theory of the case, such evidence was irrelevant

to a finding of general recognition of Fiorinal with Codeine No. 1 and Fiorinal with Codeine No. 2. *See* app., 51a-53a.

Therefore, because (1) experts could have made a determination of general recognition of FWC No. 3 different than that for the products at issue in New Jersey, and (2) the N.J. Court, due to the nature of its holding, could not adequately consider the evidence for FWC No. 3 in the context of the issue of general recognition of FWC No. 3, then the use of the New Jersey decision to estop the general recognition of FWC No. 3 is *per se* unfair.

The fact that the N.J. Court denied discovery that would still be available in Ohio exacerbates this unfairness. The Sixth Circuit found that Sandoz was correctly denied discovery by the N.J. Court because Sandoz failed to identify any undiscovered fact relevant to the "new drug" status of the products at issue in New Jersey. App., 6a. Even assuming that this conclusion is correct, it has no effect on the question of whether Sandoz should have the opportunity to conduct discovery with respect to FWC No. 3. A number of potentially discoverable facts could be relevant to the "new drug" status of FWC No. 3. For example, deposition of the government's experts could disclose the same basis expressed by Sandoz' experts for concluding that the scientific evidence supports the general recognition of effectiveness of the higher-strength FWC No. 3. The use of collateral estoppel to equate the degree of discovery permitted in unequal cases is, again, *per se* unfair. The Sixth Circuit's conclusions with respect to these *Parklane* factors in effect eliminates such factors from consideration in the application of offensive collateral estoppel; *Parklane* requires an opposite conclusion.

CONCLUSION

For the foregoing reasons, Sandoz prays that this Honorable Court grant this Petition for Writ of Certiorari and, on review, reverse the decision of the U.S. Court of Appeals for the Sixth Circuit and the U.S. District Court for the Southern District of Ohio, and remand the case for a determination on the merits.

Respectfully submitted,

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April 24, 1990

APPENDICES

APPENDIX A

UNITED STATES COURT OF APPEALS
FOR THE SIXTH CIRCUIT

No. 88-3691

UNITED STATES OF AMERICA,
Plaintiff-Appellee,

v.

SANDOZ PHARMACEUTICALS CORP.,
AND 14 BOXES, MORE OR LESS, . . .
FIORINAL WITH CODEINE NO. 3,
Defendant-Appellant.

On Appeal from the United States District Court
for the Southern District of Ohio

Decided and Filed January 25, 1990

Before: JONES and BOGGS, Circuit Judges; and COOK, District Judge*.

PER CURIAM. Defendant-appellant, Sandoz Pharmaceuticals Corporation (Sandoz), appeals from the judgment of the district court in favor of plaintiff-appellee, United States of America (Government), acting on behalf of the Food and Drug Administration (FDA), in

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* Honorable Julian A. Cook, Jr., United States District Judge for the Eastern District of Michigan, sitting by designation.

this *in rem* seizure action filed pursuant to the Federal Food, Drug and Cosmetic Act (Act), 21 U.S.C. § 301 *et seq.* (1982). For the following reasons, we affirm.

I.

Sandoz first marketed Fiorinal with Codeine (FWC)-type products in 1963, after receiving informal advice from the FDA that the products were not regarded as "new drugs." In 1968, FDA revoked all informal opinions and required manufacturers to file a "new drug application" (NDA) for any product classified as a "new drug" under 21 U.S.C. § 321(p). The NDA must be approved before a new drug may be introduced into interstate commerce. 21 U.S.C. § 355(a). An abbreviated NDA can be used for duplicates of new drugs or closely related drugs. 21 C.F.R. § 314.56 (1988).

In 1977, the FDA approved Fiorinal as a "new drug" effective for treating tension headaches. Thereafter, Sandoz sought approval of its FWC products through the abbreviated NDA procedure, contending that the FWC products were closely related to the previously approved drug, Fiorinal. FDA officials rejected Sandoz's arguments, finding that FWC products were "new drugs" requiring full NDA's. In November 1984, the FDA sent Sandoz a regulatory letter which stated that the FWC products were considered "new drugs," and that its continued marketing of FWC products without approval of a NDA would violate 21 U.S.C. § 355. Subsequently, Sandoz submitted a NDA for the FWC products and another request that the FDA accept an abbreviated NDA for these products. Upon preliminary review of the NDA, the FDA found that the application was not approvable, and also rejected Sandoz's request for an abbreviated procedure. Thereafter, Sandoz notified the FDA that it believed the FWC products were not new drugs and submitted several studies indicating that FWC products were both safe and effective. However, the FDA declined to reverse its position.

On June 17, 1986, the Government filed a complaint in the United States District Court for the Southern District of Ohio, and subsequently seized several boxes containing Fiorinal with Codeine No. 3 (FWC No. 3). Approximately four months later, the Government brought a separate complaint for forfeiture in the United States District Court for the Northern District of New Jersey, alleging that two other drugs distributed by Sandoz, Fiorinal with Codeine No. 1 and Fiorinal with Codeine No. 2 (FWC No. 1 and FWC No. 2) were "new drugs" that could not be marketed without FDA approval. After evaluating documentary evidence submitted by both parties (the same clinical evidence and testimony filed in the Ohio action), the New Jersey district court granted summary judgment to the Government, finding that FWC No. 1 and FWC No. 2 are "new drugs" within the meaning of 21 U.S.C. § 321(p). *United States v. 225 Cartons, More or Less, of an Article of Drug*, 687 F.Supp. 946 (D.N.J. 1988), *aff'd*, 871 F.2d 409 (3d Cir. 1989).

In the instant action, the Ohio district court ruled that Sandoz was collaterally estopped from relitigating the issue of whether FWC No. 3 is a "new drug." The court entered a permanent injunction and ordered that the seized articles be destroyed; however, these orders were stayed pending the outcome of Sandoz's appeals.

II.

Sandoz argues that the district court erred in finding that this action is barred by the doctrine of collateral estoppel. The availability of collateral estoppel is a mixed question of law and fact which we review *de novo*. *Plaine v. McCase*, 797 F.2d 713, 718 (9th Cir. 1986). However, once it is established that the elements of collateral estoppel are present, a district court has broad discretion to determine when the doctrine should be applied offensively. *Id.*

The doctrine of collateral estoppel may be applied only if four criteria have been satisfied:

(1) the precise issue raised in the present case must have been raised and actually litigated in the prior proceeding;

(2) determination of the issue must have been necessary to the outcome of the prior proceeding;

(3) the prior proceeding must have resulted in a final judgment on the merits; and

(4) the party against whom estoppel is sought must have had full and fair opportunity to litigate the issue in the prior proceeding.

Detroit Police Officers Association v. Young, 824 F.2d 512, 515 (6th Cir. 1987). Sandoz claims that neither the first, second, nor the fourth criteria have been satisfied.

A.

The Ohio district court properly noted that the drug at issue here (FWC No. 3) and the drugs involved in the New Jersey action (FWC No. 1 and FWC No. 2) contain four ingredients, three of which are identically formulated. The only distinction between the three drugs is the amount of the fourth ingredient, codeine. Sandoz presents two reasons why the precise issues in the Ohio case are different than those in the New Jersey action.

First, Sandoz argues that the different amounts of codeine in the FWC products require different determinations of the "new drug" status of each product. We reject this argument. Both legal actions required identical showings that each ingredient contributes to the claimed effect. In fact, in both the New Jersey and Ohio forums, Sandoz defended the efficacy of its products with the same six studies and expert declarations.[1] The New

[1] The New Jersey district court determined that four of the six studies on which Sandoz relied were not relevant to the seized

Jersey district court found that Sandoz failed to show the contributions of the non-codeine components to the efficacy of the FWC products, the same showing required for FWC No. 3 in the Ohio proceeding. This finding renders the issue of codeine's contribution to FWC No. 3 immaterial. As a result, Sandoz has no basis for its claim that the evidence for FWC No. 3 is stronger than the evidence for FWC No. 1 and FWC No. 2.

Second, Sandoz contends that the New Jersey action involved an "unmixed" question of law, or "issues of law which arise in successive actions involving unrelated subject matter." *United States v. Stauffer Chemical Co.*, 464 U.S. 165, 170 n.3 (1984) (citation omitted). In such cases, the courts do not give the legal decisions collateral estoppel effect. Sandoz notes that the instant case is based on a different cause of action, predicated on a different *res*, and presents a different legal question than the New Jersey action. As such, Sandoz claims that there must be different legal evaluations of the evidence supporting the drugs' effectiveness.

We find this argument unpersuasive. The Supreme Court has severely limited the "unmixed" question of law exception. The *Stauffer* Court noted that the exception requires a determination that the " 'issue of law' arises in a successive case that is so unrelated to the prior case that relitigation of the issue is warranted." *Id.* at 171. In the instant case, the factual and legal issues are almost identical. In both the New Jersey and Ohio actions, the Goverment seized drugs to prevent their sale and distribution pending a submission of a NDA. In addition, the judgment in both cases rested upon a determination of the validity and relevance of clinical studies, which are by *definition* fact-based evaluations, and an assessment of whether these fact-based evalua-

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articles because they tested old FWC drugs. The remaining two studies did not provide any evidence of the effectiveness of individual ingredients. 687 F.Supp. at 952-53.

tions meet the standards set forth in the FDA regulations. Thus, we find that because the New Jersey judgment was a mixed question of fact and law in an action very similar to the instant case, the application of collateral estoppel in this case was permissible.

B.

Sandoz also argues that the second and fourth criteria for collateral estoppel were not present. Sandoz first maintains that the findings of the New Jersey district court were not necessary to the outcome of that proceeding. In particular, Sandoz claims that the only finding necessary to its judgment was that there has been no study of any new formulation of FWC No. 1 or FWC No. 2 to determine the contribution of caffeine, one of the non-codeine ingredients. This argument is unpersuasive because Sandoz submitted the six clinical studies into evidence in the New Jersey action in order to defend FWC No. 1 and FWC No. 2. Having placed the studies at issue, Sandoz cannot now argue that it was unnecessary for the New Jersey district court to rule on their relevance.

Sandoz next contends that it did not have a full and fair opportunity to litigate in New Jersey because it was denied discovery. We reject this claim. The only factual issue presented by the Government's motion for summary judgment in New Jersey concerned whether there were adequate and well-controlled published clinical studies showing that the dosage of each ingredient in FWC No. 1 and FWC No. 2 contributed to the effects claimed by Sandoz for these drugs. Because Sandoz failed to identify any undiscovered essential fact relevant to this issue, to show that the denial of its discovery request was unfair, or to show that discovery could have led to a different result in either jurisdiction, we find that Sandoz had a full and fair opportunity to litigate in the New Jersey proceeding.

III.

Sandoz argues that even if the elements of collateral estoppel are present, its application in the instant case would not be fair. In *Parklane Hosiery Co., Inc. v. Shore*, 439 U.S. 322, 330-31 and n.15 (1979), the Supreme Court indicated two situations in which the application of offensive collateral estoppel can be unfair to defendants: (1) if a defendant in the first action is sued for small or nominal damages, he may have little incentive to defend vigorously; and (2) if the defendant in the first action was unable to engage in full scale discovery or call witnesses, application of offensive estoppel may be unwarranted.

Sandoz contends that it did not have an adequate incentive to defend the New Jersey action vigorously for the following three reasons: FWC No. 1 and FWC No. 2 generate lower revenues than FWC No. 3; the Ohio case was instituted before the New Jersey case; and the evidence to support FWC No. 3 was generally stronger than that supporting FWC No. 1 and FWC No. 2. Sandoz maintains that undefined time constraints and the relatively weaker case in New Jersey forced it to scale down its defense in that action.

We find these arguments unpersuasive. First, the amount of revenues at stake in the New Jersey action was not nominal, especially since sales of the drugs in question generated over three million dollars a year. Second, the record does not show that time constraints were imposed on Sandoz as a result of the New Jersey action. Finally, there is nothing in the record to indicate that the evidence presented in the New Jersey action differed from the evidence presented here. Thus, we conclude that Sandoz had ample incentive to litigate both actions vigorously as long as both actions were pending.

With respect to Sandoz's argument under the second *Parklane* situation, that full-scale discovery was not pre-

mitted, we have already concluded that the New Jersey proceeding gave Sandoz a full and fair opportunity to prove that FWC products are not "new drugs." Finally, Sandoz contends that the Government's choice of forum was unfair because it did not receive a full hearing in the New Jersey district court. However, there is no evidence that the New Jersey forum was more inconvenient than Ohio or that it deprived Sandoz of any procedural opportunities available in Ohio. *Parklane*, 439 U.S. at 332. Thus, we conclude that the application of offensive collateral estoppel against Sandoz is not unfair under the *Parklane* criteria.

IV.

Finally, Sandoz maintains that collateral estoppel is not available in the instant case because the New Jersey district court failed to decide whether FWC No. 3 fits within the *Bentex* exception. In *Weinberger v. Bentex Pharmaceuticals*, 412 U.S. 645 (1971), the Court established a limited exception to the well-controlled clinical investigations requirement. But, contrary to Sandoz's claim, the New Jersey district court fully examined this claim before rejecting it. The court stated:

> The Supreme Court [in *Bentex*] did not refer to long-used drugs as being within such an exception, and subsequent case law does not disclose any specific category of cases which would fall within this dictum. The long use situation has specifically been held not to fall within any exception to the well-controlled clinical investigations requirement.

687 F.Supp. at 959-60. Thus, Sandoz's *Bentex* claim fails.

V.

Accordingly, for above stated reasons, the judgment of the district court is AFFIRMED.

APPENDIX B

IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF OHIO
EASTERN DIVISION

Case No. C-2-86-741
JUDGE GRAHAM

UNITED STATES OF AMERICA,
Plaintiff,

vs.

An Article of Drug ". . . 14 boxes, more or less, . . .
FIORINAL WITH CODEINE NO. 3 . . ." etc.,
Defendants.

[Filed May 24, 1988]

MEMORANDUM AND ORDER

This is a civil action filed on June 17, 1986 by plaintiff, the United States of America, pursuant to the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 301 *et seq.* for the seizure and condemnation of the defendant articles of drug named in the complaint.

The drug in question has the trade name Fiorinal with Codeine No. 3, and is manufactured by Sandoz Pharmaceuticals Corp., East Hanover, New Jersey. The complaint alleges that Fiorinal with Codeine No. 3 is a new drug within the meaning of 21 U.S.C. §§ 321(g) and (p) which cannot be introduced or delivered for introduction into interstate commerce without the prior approval of an application filed pursuant to 21 U.S.C. § 355, and that no

such approval is currently in effect for that drug. The complaint asserts that the drug articles in question are being held illegally within the jurisdiction of the court and requests a decree of condemnation of the defendant articles.

On July 11, 1986, Sandoz Pharmaceuticals Corporation ("Sandoz") filed a claim of ownership of the defendant articles and asserted its right to defend the action. Sandoz, by answer filed on July 29, 1986, admitted that the drug was shipped in interstate commerce, but denied that the articles were a new drug within the meaning of 21 U.S.C. § 321(p). On December 15, 1986, Sandoz filed a motion to refer the case to the Food and Drug Administration ("FDA") for administrative hearings on the issue of whether Fiorinal with Codeine is a new drug. On February 13, 1987, plaintiff filed a memorandum in opposition to Sandoz's motion to refer the action for administrative hearings and a motion for summary judgment. Sandoz responded to plaintiff's summary judgment motion on May 15, 1987.

On March 16, 1988, plaintiff filed a motion to amend its complaint to include a prayer for injunctive relief, and a pleading entitled "Motion for Judgment." Sandoz has responded to both these motions, and they are now before the Court for decision.

Plaintiff's motion for judgment relies on the decision rendered by the United States District Court for the District of New Jersey in *United States v. Articles of Drug . . . Fiorinal with Codeine Nos. 1 and 2*, unpublished opinion, Civil No. 86-3877 (March 8, 1988) and on the final judgment filed in that case on April 18, 1988. The New Jersey case was also a seizure and condemnation action under 21 U.S.C. § 301 *et seq.*, with the government as plaintiff and Sandoz as claimant. The articles of drug named as defendants were Fiorinal with Codeine Nos. 1 and 2. The New Jersey court granted the plain-

tiff's motion for summary judgment in that case and entered final judgment in favor of the plaintiff. Plaintiff contends that the principles of collateral estoppel should now bar Sandoz from relitigating issues decided adversely to Sandoz in the New Jersey action, and that the resolution of those issues by the New Jersey court dictates that judgment likewise be entered for plaintiff in this case. While the Federal Rules of Civil Procedure make no provision for a "Motion for Judgment," it is appropriate to raise the issue of res judicata in a motion for summary judgment. *Smith v. United States*, 369 F.2d 49 (8th Cir. 1966). Since the parties refer to materials outside the pleadings in arguing the motion, the Court will regard the motion for judgment as an amendment to plaintiff's previous summary judgment motion.

Federal courts have long recognized and applied the preclusion doctrines of res judicata and collateral estoppel. A fundamental precept of common-law adjudication is that an issue once determined by a competent court is conclusive. *Arizona v. California*, 460 U.S. 605 (1983). In *Federated Department Stores, Inc. v. Moitie*, 452 U.S. 394, 401 (1981), the Supreme Court commented:

> "Simple justice" is achieved when a complex body of law developed over a period of years is even-handedly applied. The doctrine of res judicata serves vital public interests beyond any individual judge's ad hoc determination of the equities in a particular case. There is simply "no principle of law or equity which sanctions the rejection by a federal court of the salutary principle of *res judicata*." *Heiser v. Woodruff*, 327 U.S. 726, 733 (1946). . . . This Court has long recognized that "[p]ublic policy dictates that there be an end of litigation; that those who have contested an issue shall be bound by the result of the contest, and that matters once tried shall be considered forever settled as between the parties." *Baldwin v. Traveling Men's Assn.*, 283 U.S. 522, 525

> (1931). We have stressed that "[the] doctrine of *res judicata* is not a mere matter of practice or procedure inherited from a more technical time than ours. It is a rule of fundamental and substantial justice, 'of public policy and of private peace,' which should be cordially regarded and enforced by the courts. . . ." *Hart Steel Co. v. Railroad Supply Co.*, 244 U.S. 294, 299 (1917).

Under the doctrine of collateral estoppel, once an issue is actually and necessarily determined by a court of competent jurisdiction, that determination is conclusive in subsequent suits based on a different cause of action involving a party to the prior litigation. *Montana v. United States*, 440 U.S. 147 (1979).

The present case involves an offensive rather than defensive use of collateral estoppel, that is, it is the prevailing plaintiff in the prior litigation who now seeks to invoke collateral estoppel. In *Parklane Hosiery Co. v. Shore*, 439 U.S. 322 (1979), the Supreme Court granted trial courts broad discretion in the application of offensive collateral estoppel. However, the Court discussed factors to be considered in making that determination. The Court noted first that the invocation of offensive collateral estoppel would have the effect of encouraging multiple plaintiffs to await the outcome of litigation between the defendant and other plaintiffs rather than joining in the litigation, thus fostering rather than discouraging multiple lawsuits. *Id.* at 329-330. The Court further noted that applying collateral estoppel offensively might be unfair to the defendant, in that a defendant who is sued in the first action for nominal damages may lack incentive to defend vigorously, particularly if future suits are unlikely. *Id.* at 330. Finally, offensive collateral estoppel might be unfair to a defendant if the judgment relied on is inconsistent with previous judgments in favor of defendant, or if the pending action affords defendant procedural opportunities which were unavailable

in the first action that could lead to a different result. *Id.* at 330.

None of the considerations which concerned the Court in *Parklane Hosiery* are present in the case at bar. Both the New Jersey case and the present action are seizure proceedings brought by the government. The government is the only possible plaintiff in such an action. This action was filed on June 17, 1986, and thus Sandoz has been aware of its pendency while litigating the New Jersey case. The parties have not informed the court of any previous inconsistent judgment, and no procedures are available in this Court that were not available to Sandoz in the New Jersey litigation. The Court finds that the offensive use of collateral estoppel would not work an injustice in this case.

It remains to be determined whether the elements of collateral estoppel have been satisfied in this case. The following elements, as set forth in *N.A.A.C.P., Detroit Branch v. Detroit Police Officers Association*, 821 F.2d 328, 330 (6th Cir. 1987), must be met before collateral estoppel may be applied to bar litigation of an issue:

> (1) the precise issue raised in the present case must have been raised and actually litigated in the prior proceeding;
>
> (2) determination of the issue must have been necessary to the outcome of the prior proceeding;
>
> (3) the prior proceeding must have resulted in a final judgment on the merits; and
>
> (4) the party against whom estoppel is sought must have had a full and fair opportunity to litigate the issue in the prior proceeding.

In regard to the first element, Sandoz argues that the New Jersey court did not decide the same issues pending before this Court because the substances named as defendants in the complaint are different. The New Jersey

action involved Fiorinal with Codeine Nos. 1 and 2, while this case involves Fiorinal with Codeine No. 3. The record reveals that all Fiorinal with Codeine products contain the same ingredients, specifically three hundred and twenty-five milligrams of aspirin, forty milligrams of caffeine, fifty milligrams of butalbital, and codeine. The only difference in the components of the products is the amount of codeine contained in each preparation. Fiorinal with Codeine Nos. 1, 2 and 3 contain seven point five, fifteen and thirty milligrams of codeine respectively.

The issue before the New Jersey court was whether Fiorinal with Codeine is a new drug within the meaning of 21 U.S.C. § 321(p), so that its introduction into interstate commerce without approval of a new drug application pursuant to 21 U.S.C. § 335(b) is a violation of 21 U.S.C. § 355(a). Sandoz has not contested the fact that the FDA has not approved a new drug application for Fiorinal with Codeine, but denies that Fiorinal with Codeine is a new drug under 21 U.S.C. § 321(p). A "new drug" is defined as a drug "the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed. . . ." 21 U.S.C. § 321(p).

The New Jersey court addressed the question of whether a genuine issue of fact was shown concerning the general recognition of Fiorinal with Codeine Nos. 1 and 2 among experts as being effective, including whether each component of the two products contributes to their effectiveness. The New Jersey court held that in order to avoid summary judgment, Sandoz had the burden of demonstrating a genuine issue of fact through the existence of substantial evidence of effectiveness, that is, "adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of

the drug involved" as required by 21 U.S.C. § 355(d). *United States v. Articles of Drug . . . Fiorinal with Codeine Nos. 1 and 2,* (Opinion p. 32.)

The New Jersey court held that Sandoz could not rely on older clinical studies conducted with the former Fiorinal with Codeine (which contained the extra ingredient phenacetin) or with certain other preparations since bioequivalency between the present Fiorinal with Codeine Nos. 1 and 2 and the substances studied was not demonstrated. (Opinion p. 36). The court found that: 1) there had been no study of Fiorinal with Codeine No. 1 with respect to its overall efficacy or its components; 2) there had been no study on any formulation of Fiorinal with Codeine to determine the contribution of forty milligrams caffeine; 3) the only study as to the effect of butalbital was on the old form of Fiorinal with Codeine No. 2, not shown to be bioequivalent; 4) the only study concerning the contribution of codeine to the product's effectiveness was conducted with the old formulation of Fiorinal with Codeine No. 3; and 5) the only study involving the current Fiorinal with Codeine No. 3 did not analyze the contribution of the components. (Opinion pp. 37-38) The court went on to hold that Sandoz had failed to show a genuine issue of material fact as to the reputation for effectiveness of Fiorinal with Codeine Nos. 1 and 2, and that those substances were therefore new drugs, and granted summary judgment in favor of the plaintiff on the seizure complaint.

Several of the findings made by the New Jersey court involve the identical issues before this court. The lack of any study to determine the contribution of forty milligrams caffeine applies equally to Fiorinal with Codeine No. 3, as does the lack of studies concerning the contribution of butalbital. While the judgment of the New Jersey court did not specifically encompass Fiorinal with Codeine No. 3, the legal issues resolved by the court,

particularly in regard to the non-codeine components of Fiorinal, which are identical regardless of the amount of codeine in the preparation, are the exact issues before this Court. The New Jersey court's findings as to these non-codeine components were not dependent upon or determined by the amount of codeine present and thus apply equally to Fiorinal with Codeine No. 3.

The determination of the sufficiency of the studies submitted in the summary judgment proceedings was necessary to the outcome of those proceedings. In order to decide if Sandoz had shown a genuine issue of fact concerning whether Fiorinal was reputed to be effective and therefore not a new drug requiring approval, the court had to resolve whether the clinical studies relied upon by Sandoz tended to show the effectiveness of Fiorinal and its various components. Thus, the second element of collateral estoppel was satisfied.

The New Jersey court entered final judgment on behalf of the plaintiff following the award of summary judgment. A grant of summary judgment which disposes of a case completely is considered a judgment on the merits for purposes of *res judicata*. *Hufsmith v. Weaver*, 817 F.2d 455 (8th Cir. 1987); *Spiegel v. Continental Illinois Nat'l Bank*, 790 F.2d 638 (7th Cir. 1986).

Finally, Sandoz had a full and fair opportunity to litigate the issue in the summary judgment proceedings before the New Jersey court. Sandoz claims that it was denied the opportunity to obtain discovery or to cross-examine the experts relied upon by the government. However, the New Jersey court determined that the additional discovery sought by Sandoz was irrelevant to the proceedings and would not fill the void in published clinical investigations. (Opinions, p. 39) Similarly, the lack of opportunity to cross-examine the plaintiff's experts would have no effect on the lack of clinical studies upon which the New Jersey court based its decision. The New Jersey court denied Sandoz's motion to refer

the case to the FDA for the development of an administrative record. The New Jersey court found that such a procedure was not required by the seizure statute. In addition, there is no indication that the administrative hearing would have revealed additional studies not already within the knowledge of the parties.

In summary, all of the elements necessary for the application of collateral estoppel have been satisfied in this case. Sandoz argues that invoking collateral estoppel would nonetheless be inappropriate because the New Jersey court's resolution of the case before it was legally erroneous. The preclusive effect of a final judgment is not altered by the fact that the judgment may be wrong. *Federated Department Stores, Inc. v. Moitie, supra* at 398. A judgment on the merits, even if erroneous, will be deprived of its conclusive effect only if it is vacated, reversed or set aside on direct appeal. *Dodrill v. Ludt*, 764 F.2d 442 (6th Cir. 1985); *Harrington v. Vandalia-Butler Bd. of Educ.*, 649 F.2d 434 (6th Cir. 1981). The mere pendancy of an appeal does not diminish the res judicata effect of a trial court's judgment. *Eichman v. Fotomat Corp.*, 759 F.2d 1434 (9th Cir. 1985).

The Court finds that Sandoz is collaterally estopped from relitigating the issue of whether Fiorinal with Codeine No. 3 is a new drug in light of the findings of the New Jersey District Court, upon entering summary judgment for plaintiff, that Sandoz failed to produce the necessary clinical studies to show that Fiorinal with Codeine was generally reputed to be effective, and therefore failed to show it is not a new drug. The findings by the New Jersey court dictate that Fiorinal with Codeine No. 3 is a new drug which requires prior approval of a new drug application before it can be shipped in interstate commerce. The defendant articles were shipped in interstate commerce without FDA approval, and therefore the defendant articles of drug are subject to seizure and condemnation. The New Jersey court

has also resolved the issue of the necessity of prior administrative hearings by the FDA against Sandoz, and therefore, Sandoz is estopped from further arguing the defense here. In any event, this Court is in agreement with the New Jersey court's resolution of that question.

Summary judgment is hereby AWARDED to plaintiff.

Plaintiff has also filed a motion to amend the complaint to include a prayer for injunctive relief. Under Fed. R. Civ. P. 15(a), leave to amend a complaint "shall be freely given when justice so requires." In the absence of undue delay, bad faith or dilatory motive, or undue prejudice to the opposing party, leave to amend should be liberally granted. *Foman v. Davis*, 371 U.S. 178 (1962). The decision whether to allow amendment rests within the discretion of the trial court. *Duchon v. Cajon Co.*, 791 F.2d 43 (6th Cir. 1986).

The Court hereby GRANTS plaintiff's motion to amend the complaint. There is no evidence of bad faith or improper motive on the part of plaintiff in requesting the amendment, and Sandoz has not shown that granting the motion would result in undue prejudice.

In regard to the question of the merits of injunctive relief, the Court notes that the parties have not yet fully briefed this issue. The Court further notes that since the filing of the motion to amend the complaint, the parties reached an agreement on the issue of injunctive relief in the New Jersey litigation. Thereafter, the Court will await further briefing before deciding this issue on the merits. Plaintiff's brief shall be due fifteen days from the date of this Order. Sandoz shall have fifteen days from the filing of plaintiff's brief to respond. If the parties are able to reach an agreement on the issue of injunctive relief, they shall notify the Court immediately so that an appropriate Order may be entered.

It is so ORDERED.

/s/ James L. Graham
JAMES L. GRAHAM
United States District Judge

DATE: May 24, 1988

IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF OHIO
EASTERN DIVISION

Case No. C-2-86-741
JUDGE GRAHAM

UNITED STATES OF AMERICA,
Plaintiff,

vs.

An Article of Drug ". . . 14 boxes,
more or less, . . . FIORINAL WITH
CODEINE No. 3 . . ." etc.,
Defendants.

[Filed June 22, 1988]

JUDGMENT ENTRY

It is hereby Adjudged that plaintiff's motion for summary judgment is GRANTED and judgment is hereby awarded to plaintiff.

It is hereby Ordered that the defendant articles of drug, being a new drug within the meaning of 21 U.S.C. § 355 which has not been approved by the Food and Drug Administration and which has been unlawfully shipped in interstate commerce under the provisions of 21 U.S.C. § 331(d), are to be destroyed by the United States Marshal.

It is further Ordered that defendant Sandoz Pharmaceuticals Corp. is hereby enjoined from distributing or shipping Fiorinal with Codeine No. 3 in interstate com-

merce, and that said injunction will remain in force and effect for as long as Fiorinal with Codeine No. 3 remains a new drug within the meaning of 21 U.S.C. § 355 which has not been approved according to law by the Food and Drug Administration for distribution.

It is further Ordered that enforcement of this Court's judgment consisting of orders for destruction of the seized articles of drug and for an injunction against the distribution or shipment of Fiorinal with Codeine No. 3 is hereby stayed pursuant to Fed. R. Civ. P. 62 until decisions are rendered by the Third Circuit Court of Appeals in Sandoz's appeal from the court's order in *United States v. Articles of Drug . . . Fiorinal with Codeine Nos. 1 and 2*, Civil No. 86-3877 (D. New Jersey), and by the Sixth Circuit Court of Appeals in Sandoz's appeal from the instant judgment.

Date June 22, 1988

KENNETH J. MURPHY
Clerk

/s/ [Illegible] Robinson
(By) Deputy Clerk

APPENDIX C

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

Civ. A. No. 86-3877

UNITED STATES OF AMERICA,
Plaintiff,

v.

225 CARTONS, MORE OR LESS, OF AN ARTICLE OF DRUG, each carton containing 12/100 capsule bottles, labeled in part:

(carton)

"* * * Sandoz Pharmaceuticals East Hanover, NJ 07936 * * *" with an area cut out showing bottle labeling described below

(bottle)

"* * * Fiorinal with Codeine No. 1 * * *
Sandoz Inc. East Hanover, NJ * * *"

(insert attached to bottle)

"Fiorinal with Codeine Capsules * * *"

144 packages, more or less, of an article of drug, each package containing 12/100 capsule bottles and covered by an unlabeled, see-through, cellophane overwrap, labeled in part:

(bottle)

"* * * Fiorinal with Codeine No. 2 * * *
Sandoz Inc. East Hanover, NJ * * *"

(insert attached to bottle)

"Fiorinal with Codeine Capsules * * *"

4,780 blister packs, more or less, of an article of drug, each blister pack containing 20 capsules and one insert, labeled in part:

(blister pack)

"* * * Fiorinal with Codeine No. 2 Sample * * *
Sandoz, Inc. East Hanover, NJ 07936 * * *"

and

undetermined quantities of the articles of drug Fiorinal with Codeine No. 1 and Fiorinal with Codeine No. 2, packaged and labeled as described above,

Defendants.

March 8, 1988

OPINION

DEBEVOISE, District Judge.

I. *The Proceedings*

Plaintiff is the United States which instituted this action on behalf of the Food and Drug Administration (FDA). The defendants are two prescription drug products, FIORINAL WITH CODEINE NO. 1 and NO. 2 (FWC No. 1 and FWC No. 2). The claimant is Sandoz Pharmaceutical Corporation (Sandoz) which manufacturers and distributes the FWC products.

This is an in rem seizure action brought under 21 U.S.C. § 334. The complaint for forfeiture alleges that the seized FWC No. 1 and FWC No. 2 are "new drugs" within the meaning of 21 U.S.C. § 321(p) which may not, without violating 21 U.S.C. § 355(a), be introduced into interstate commerce because a new drug application (NDA) has not been approved by the FDA pursuant to 21 U.S.C. § 355(b). Further, the complaint alleges that the FWC products are misbranded within the meaning of 21 U.S.C. § 352(f)(1) because their labeling fails to bear adequate directions for use, and they are not exempt

from this requirement because they are unapproved "new drugs".

After the drugs were seized by the United States Marshal pursuant to court order, Sandoz intervened and filed a claim. In its answer it admitted that the court has jurisdiction, that the seized articles are drugs located within the jurisdiction of the court and that the seized articles were manufactured from one or more components which were shipped in interstate commerce. Sandoz denied that the FWC products are "new drugs" within the meaning of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 301, et seq. (the FDC Act) and that they are misbranded. Further, Sandoz defended on the ground that the case must be dismissed because the FDA did not develop an administrative record pursuant to 5 U.S.C. § 554 before it filed its complaint for forfeiture.

The FDA moved for summary judgment. It contends that to obtain judgment on the "new drug" charge it need only establish (i) that no NDA for the FWC products has been approved by the FDA (which Sandoz will admit) and (ii) that the FWC products are "new drugs". The FDA further contends that to obtain judgment on the misbranding charge it need only prove the same two facts and that the FWC products are prescription drugs (which Sandoz will admit). Thus, according to the FDA, the only contested issue is whether the FWC product is a new drug. The FDA submitted in support of its summary judgment motion exhibits and declarations of experts which, it contends, establish that there is no genuine issue of material fact and that the FWC product is indeed a new drug.

In response to FDA's motion Sandoz submitted declarations to support its contention that FWC No. 1 and FWC No. 2 are not new drugs and it moved pursuant to Fed.R.Civ.P. 56(f) for a continuance to permit discovery to oppose the motion for summary judgment.

II. *The Applicable Statute and Regulations*

The FDA Act establishes a system for the premarket clearance of drug products. 21 U.S.C. § 355. Under the Act as adopted in 1938, 52 Stat. 1040, no new drug could lawfully be introduced into commerce unless and until an NDA for that product had been filed with and approved by the FDA. See 21 U.S.C. § 355(a), 52 Stat. 1052. The 1938 Act defined a new drug as any product which, among other things, was not "generally recognized" by qualified experts as *safe* for its intended use. See § 201(p), 52 Stat. 1041.

Congress adopted amendments to the FDA Act in 1962. See Drug Amendments of 1962, Pub.L. No. 87-781, 76 Stat. 780. Under the 1962 amendments manufacturers were required to show that a new drug product was *effective* as well as safe for its intended use. 21 U.S.C. § 355(a) and (b). A "new drug" was defined as "[a]ny drug . . . the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof. . . ." 21 U.S.C. § 321(p).

Under the 1962 amendments a manufacturer seeking approval of an NDA was required to submit "substantial evidence" of the product's safety and effectiveness. The statute defined "substantial evidence" as "evidence consisting of adequate and well-controlled investigations, including clinical investigations . . . on the basis of which it could fairly and responsibly be concluded . . . that the drug will have the effect it purports . . . to have under the conditions of use prescribed . . . in [its] labeling. . . ." 21 U.S.C. § 355(d). Sandoz FWC products are exempt from the FDA's premarket clearance procedures only if they are "generally recognized" as safe and effective for their intended uses. 21 U.S.C. § 321(p).

The 1962 amendments required the FDA to evaluate the effectiveness of all drug products, not grandfathered, which had been placed on the market since 1938. To do this, the FDA enlisted the services of the National Academy of Sciences—National Research Council (NAS-NRC), which, after investigation, made recommendations to the FDA regarding the effectiveness of therapeutic classes of products. As the FDA reviewed the NAS-NRC recommendations, it published drug efficacy study implementation (DESI) notices in the Federal Register which rated products as to their effectiveness for specific labeled indications. Products that were found to be effective were still regarded as new drugs and manufacturers were required to supplement their NDAs to conform to conditions imposed by the DESI notices. In the period shortly after adoption of the 1962 amendments the FDA issued informal opinions with respect to some drug products that they found were not new drugs. However, in 1968 the FDA adopted a regulation revoking all such opinions. 21 C.F.R. § 310.100(d). Thereafter virtually all prescription drug products which had come on the market since 1938 would be regarded as a new drug requiring either a full or, in certain narrowly defined cases, an abbreviated new drug application (ANDA).

In 1976 the FDA published a Compliance Policy Guide (CPG) which established enforcement priorities for proceedings against DESI-related drugs that were being marketed without approved applications. The sixth category included unapproved combination drugs that are related to drugs which had been found effective in the DESI program.

As noted above before a product can be exempted from the statutory, new drug preclearance procedures, it must be "generally recognized" by qualified experts as safe and effective for its intended uses. 21 U.S.C. § 321(p). The "general recognition" requirement does not involve the actual safety or effectiveness of the product. Rather,

it is the product's reputation in the scientific community that is relevant. Further, the experts' opinion as to general recognition must be based upon well-controlled, clinical studies which are published; the opinions of experts may not be based upon uncontrolled data or upon their own personal experiences. *Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 619, 93 S.Ct. 2469, 2478, 37 L.Ed.2d 207 (1973). The general recognition of a product's safety and effectiveness must be documented by at least the same quality and quantum of evidence that would suffice to obtain FDA's approval of the product in the first instance. *Weinberger v. Bentex Pharmaceuticals, Inc.*, 412 U.S. 645, 652, 93 S.Ct. 2488, 2493, 37 L.Ed.2d 235 (1973).

Certain FDA regulations are particularly pertinent to the present case. One is contained in 21 C.F.R. § 314.126. It sets forth in considerable detail the essential compoents of an adequate and well-controlled investigation. A study must meet these criteria in order to constitute substantial evidence of a product's effectiveness. *Weinberger v. Hynson, Westcott & Dunning, Inc., supra,* 412 U.S. at 617-20, 93 S.Ct. at 2477-78; *Cooper Laboratories, Inc. v. FDA*, 501 F.2d 772 (D.C.Cir.1974).

Another particularly pertinent regulation is set forth in 21 C.F.R. § 300.50 and provides in part:

> (a) Two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug.

These, then, are the statutory and regulatory provisions which must be applied in determining the critical factual issue in the case, namely, whether FWC No. 1

and FWC No. 2 are generally recognized on the basis of well-controlled, published clinical studies to be safe and effective for their intended use.

III. *The FWC Products*

Fiorinal is an analgesic marketed by Sandoz. Originally it contained the peripheral analgesic aspirin (200 mg), phenacetin (130 mg), the analgesic adjuvant caffeine (40 mg) and the barbituate butalbital (50 mg). In 1983 pursuant to an FDA directive pertaining to products containing phenacetin, the phenacetin was removed and the quantity of aspirin was increased to 325 mg.

The FWC products consists of the Fiorinal ingredients plus varying amounts of codeine. FWC No. 1 contains 7.5 mg codeine; FWC No. 2 contains 15 mg codeine; FWC No. 3 (which is not a subject of seizure in the present case) contains 30 mg codeine. When phenacetin was removed from Fiorinal it was also removed from the FWC products. FWC is a widely prescribed combination product useful for severe tension headaches, post-surgical pain, and other forms of pain.

In 1962 Sandoz received from the FDA an informal written opinion that the FWC products were not new drugs. In July 1963 Sandoz began marketing FWC. In 1968 the FDA revoked all its informal opinions. 21 C.F.R. § 310.100(d).

In response to a 1973 DESI notice Sandoz submitted data to support its NDA for Fiorinal, but did not submit any data for its FWC products. On November 15, 1977, in response to this submission, the FDA published a DESI follow-up notice which stated that Fiorinal "has been evaluated as effective for . . . tension . . . headache" and that "[s]uch drugs are regarded as new drugs (21 U.S.C. § 321(p)."

In 1977 and 1978 Sandoz filed ANDAs with the FDA for its FWC products, the difference between an ab-

breviated and full NDA being that the aggreviated application need not contain full reports of clinical studies to prove the product's safety and effectiveness. 21 C.F.R. § 314.55(a). On both occasions the FDA rejected the applications because it had not made a specific finding that such short-form applications were appropriate for the FWC products and because the approved products, plain Fiorinal and Trigesic with Codeine, upon which Sandoz sought to "piggy back" its ANDA applications for the FWC products, contained different ingredients from the FWC products. FWC contains codeine; Fiorinal does not. FWC contains butalbital; Trigesic with Codeine does not.

Sandoz did not appeal these decisions but in 1978 filed a Notice of Claimed Investigational Exemption for a New Drug (IND). The IND has been maintained since that date.

In March 1978 FDA officials informed Sandoz that the FWC products were new drugs, requiring a full NDA. Sandoz was also informed, among other things, of the studies that would be required for approval of an NDA and that FWC No. 1 containing 7.5 mg codeine would probably not show effectiveness.

A June 24, 1980 FDA DESI order stated that no evidence had been presented to show that two products containing butalbital, acetaminophen and other analgesics were effective. On November 15, 1984 FDA sent Sandoz a Regulatory Letter reminding it that the FWC products were regarded as new drugs, that the FWC products were identical, similar or related to the barbiturate-analgesic combination drug product found to lack substantial evidence of effectiveness in the June 24, 1980 DESI order, and that continued marketing of the FWC products without an approved NDA would violate 21 U.S.A. § 355.

By letters dated December 5, 1984 and January 11, 1985, Sandoz responded to the November 15, 1984 regu-

latory letter and asked that the agency not take immediate regulatory action against FWC and further requested that the FDA allow FWC products to remain on the market pending review and approval of a soon-to-be submitted NDA. On February 1, 1985 Sandoz submitted an NDA for the FWC products.

On February 20, 1985 Sandoz submitted a third request that the FDA accept an ANDA for the FWC products, stating among other things that "Fiorinal with Codeine is identical to . . . Fiorinal with the exception of a single active ingredient, codeine phosphate, . . . the ingredients of Fiorinal with Codeine are in the same therapeutic class as the ingredients in Fiorinal, [and] there are ample data to establish that the addition of codeine to . . . Fiorinal can be expected to have the same effect as Fiorinal."

On April 16, 1985 the FDA advised Sandoz that a preliminary review of its NDA for the FWC products indicated that the application was not approvable.

On April 26, 1985 Sandoz wrote the FDA and advised that it was taking the position that the FWC products were not new drugs. It cited a long history of safe and effective use and referred to "an extensive series of clinical investigations which have given rise to a general recognition of the safety and effectiveness of the product and the contribution thereto of each of its active components."

The April 26 letter was accompanied by the declarations of Dr. Donald Dalessio and Dr. Neil Raskin. Dr. Dalessio based an opinion about the safety and effectiveness of FWC products upon his experience in prescribing the drug for a 15 year period and upon published and unpublished material which Sandoz provided him. He referred specifically to the published studies of MacDonald and Ehrenreich and of Madore and Chiricosta and to a Sandoz multi-center study which had been submitted to the FDA in support of Sandoz' NDA.

On May 16, 1985 Sandoz submitted to the FDA the declaration of Dr. Arnold P. Friedman attesting to the general recognition of the safety and effectiveness of FWC products. None of the three declarations which Sandoz submitted differentiated between the three FWC formulations.

On October 3, 1986 the complaint in this action was filed and on January 12, 1987 the United States Marshal seized the FWC products.

IV. *The Published Clinical Studies*

The critical issue in this case is whether Sandoz' FWC products are generally recognized among qualified experts as safe and effective. Safety does not appear to be a contested issue, and thus the present inquiry is confined to the FWC products' effectiveness and to the effectiveness of each of their constituent drugs. The opinions of the experts as to general recogniaton must be based upon well-controlled clinical studies which are published. The parties in this proceeding refer to six such studies in support of and in opposition to the motion for summary judgment.

A. *Madore, P. and Chiricosta, A., "Analgesic Effect of Fiorinal with Codeine," Anesthesia and Analgesia, Vol. 46, No. 4 July-Aug. 1967:* This study used FWC No. 3 which contained 30 mg of codeine. The FWC No. 3 formulation differed from that which is presently marketed in that it contained 130 mg phenacetin and 200 mg aspirin. Today's FWC No. 3 (like today's FWC No. 1 and No. 2) contains no phenacetin and 325 mg aspirin.

In the Madore and Chiricosta study 41 patients who had undergone various types of operations and complained of acute pain episodes were given, in double-blind, single dose, random-sequence fashion, one of three treatments: (a) placebo, (b) one capsule FWC No. 3, or (c) two capsules FWC No. 3. Thereafter, at hourly

intervals and for 6 hours each patient's pain relief was evaluated. The authors concluded that both quantities of active drugs were superior to placebo at hours 2 through 4, and that two capsules of FWC No. 3 were superior to one capsule of the same product only at the first hour.

B. *MacDonald, C. and Ehrenreich, K.A., "A Double-Blind Comparison of Two Analgesics with Placebo Control," Canadian Med. Assoc. J. 95:1072-75, Nov. 19, 1966:* This study compared two codeine combination analgesics prescribed in the 1960s. One was FWC No. 2 as then formulated which contained butalbital (50 mg), phenacetin (130 mg), caffeine (40 mg), aspirin (200 mg) and codeine (16 mg). The other product, APC with Codeine, contained all of those ingredients except butalbital. One purpose of the study was to assess the contribution of butalbital.

In this study pain relief was measured in 83 post-surgical patients who reported a total of 206 episodes of severe or moderate pain. Patients estimated their level of post-operative pain just prior to treatment and their pain relief approximately one hour after treatment. Three treatments were asssigned randomly to 206 severe or moderate pain episodes.

FWC No. 2 (having butalbital) provided greater pain relief than APC with Codeine (having no butalbital) in moderate and severe pain episodes and both were more effective than placebo.

C. *Desjardins, P.J., Cooper, S.A., and Finizio, T., Efficacy of Low Dose Combination Analgesics: Acetaminophen/Codeine, Aspirin/Butalbital/Caffeine/Codeine, and Placebo in Oral Surgery Pain," Anesth.Prog. 1986, May-June, 33(3):143-6:* This was a double-blind, randomized, single-dose study performed to compare the efficacy and safety of two combination analgesic products to placebo. The products were Tylenol with Codeine No. 3 con-

taining acetaminophen (300 mg) and codeine (30 mg) and FWC No. 3 containing aspirin (325 mg), butalbital (50 mg), caffeine (40 mg) and codeine (30 mg). The study showed that FWC No. 3 was significantly more effective than placebo for total pain relief, peak relief and global evaluation. FWC No. 3 was numerically superior to Tylenol with Codeine No. 3 for every measure of analgesic efficacy but the difference did not achieve statistical significance. The report stated, "[w]hether the slight improvement in analgesic is therapeutically exploitable or whether it can be attributable to a caffeine or butalbital effect cannot be answered in the present study design."

D. *Forbes, J.A., Jones, K.F., Smith, W.K., and Gongloff, C.M., "Analgesic Effect of an Aspirin-codeine-butalbital-caffeine Combination and an Acetaminophen-codeine Combination in Postoperative Oral Surgery Pain," Pharmacotherapy 1986, Sept.-Oct. (6)5:240-47:* This study was a randomized, double-blind, placebo-controlled comparison between current formulas FWC No. 2 and Tylenol with Codeine No. 3. The efficacy of FWC No. 2 was compared to Tylenol with Codeine No. 3 and placebo in outpatients who had moderate or severe pain after the surgical removal of impacted third molars.

The report stated, among other things:

> . . . Although the rationale for many combinations, for example, aspirin and codeine, is readily apparent, other combinations have less surface validity. One such combination is that of aspirin 325 mg, caffeine 40 mg, codeine phosphate 15 mg with butalbital 50 mg, a barbituate. . . . The butalbital constituent of this combination is presumed to decrease anxiety and act as a muscle relaxant.
>
> MacDonald et al demonstrated the statistical superiority of an aspirin-phenacetin-caffeine-codeine-butalbital combination to the combination without butalbital in the treatment of postoperative pain.

> The study, however, did not attempt to measure the effect, if any, of the medications on anxiety or relaxation. Although the study was conducted double-blind and employed a concomitant placebo control group, it was unusual in that (1) patients could participate more than once, (2) only one measure of effect, pain relief, was used, and (3) patients were evaluated only once, that is, at one time point, after the administration of the study medication.

The Forbes study leads to the conclusions that each medication was significantly superior to placebo for measures of analgesia and relaxation and that although the butalbital containing combination provided consistently greater analgesia, the differences between the active medications were not statistically significant. The report further stated that "[o]ne can only speculate as to the relative contribution of the constituents of these combinations since a factorial study was not conducted."

E. *Friedman, A.P., et al., "Assessment of Fiorinal with Codeine in the Treatment of Tension Headache," Clinical Therapeutics, Vol. 8, No. 6, 703-21, 1986:* This was a double-blind, randomized multi-center study in which 39 patients with specific symptoms of tension headache (pain, psychic tension, and muscle-stiffness) and 15 patients with any two of those symptoms were given one of four treatments: the early version of FWC No. 3 (containing phenacetin and 200 mg aspirin); the early version of plain Fiorinal (also containing phenacetin and 200 mg aspirin); codeine phosphate (30 mg); or placebo. Before taking one of these treatments and at .5, 1, 2, 3 and 4 hours following treatment patients rated six items on a four point scale. The physicians also made global evaluations of the effectiveness of treatment.

FWC No. 3 was found to be generally significantly more effective than placebo or Fiorinal alone in improving all patient-evaluated items between the second and fourth hours after administration. FWC No. 3 was also

found to be generally significantly better than codeine alone with respect to pain severity, pain relief, the ability to perform daily activities and average pathology. The three variables rated by the physicians also were found to be generally reduced significantly more with FWC No. 3 than with placebo or Fiorinal alone.

F. *Dar-shong Hwang, Ph.D., et al., "Fiorinal with Codeine in the Management of Tension Headache: Impact of Placebo Response," Clinical Therapeutics, Vol. 9 No. 2, 1987:* This study analyzed a subset of 67 patients admitted under a protocol identical to the Friedman, et al., study. It compared the old Fiorinal (containing phenacetin and 200 mg aspirin), the old FWC No. 3 (containing phenacetin and 200 mg aspirin), codeine and placebo. The report noted that "[i]n the original analysis of the study data, no distinction was apparent between patient response to Fiorinal with Codeine and the response to the individual components, a finding that appeared to conflict with the results of a similar earlier study." The authors of the report attributed the discrepancy to a high placebo response in the later study. To adjust for this factor they identified a subset of less anxious patients with mild to moderate pain severity who, according to the authors, were least likely to respond to placebo.

Based on the data from this less anxious subset of patients the authors found that FWC No. 3 was significantly better than placebo in improving patients' self-ratings of various symptoms of tension headache at 0.5, 1, 2, 3, and 4 hours after ingestion of the study medication and that FWC No. 3 was also consistently superior to Fiorinal alone and codeine alone in improving patients' self-evaluation items, and differences between FWC No. 3 and its components were generally of statistical or borderline significance during the last half of the study.

The investigators' assessments of the effect of treatment on the three principal variables in tension head-

ache (headache pain, psychic tension, and muscle contraction of the head, neck and shoulders) at the final patient visit also showed FWC No. 3 to be significantly superior to placebo and consistently superior to Fiorinal and codeine. The superiority of FWC No. 3 over Fiorinal alone achieved borderline significance for headache pain and psychic tension.

V. *Summary Judgment Standards*

In order to prevail on a motion for summary judgment, a moving party must establish that "there is no genuine issue as to any material fact and that [it is] entitled to a judgment as a matter of law." Fed.R.Civ.P. 56(c). The moving party has the initial burden of informing the court of the basis of its motion and identifying those portions of the record which it believes demonstrate the absence of a genuine issue of material fact. *Celotex Corp. v. Catrett*, 477 U.S. 317, 106 S.Ct. 2548, 91 L.Ed.2d 265 (1986).

Once the moving party has carried its burden under Rule 56, "its opponent must do more than simply show that there is some metaphysical doubt as to the material facts." *Matsushita Electric Industrial Co., Ltd. v. Zenith Radio Corp.*, 475 U.S. 574, 106 S.Ct. 1348, 1356, 89 L.Ed.2d 538 (1986). A plaintiff opposing a summary judgment motion must set forth specific facts showing a genuine issue of material fact. "[T]he inferences to be drawn from the underlying facts . . . must be viewed in the light most favorable to the party opposing the motion." *Id.* 106 S.Ct. at 1357. However, the *Matsushita* Court explained that in evaluating the evidence presented, "[w]here the record taken as a whole could not lead a rational trier of fact to find for the nonmoving party, there is no 'genuine issue for trial.'" 106 S.Ct. at 1356.

In addition, should it appear from the affidavits of a party opposing the motion that the party cannot for rea-

sons stated present by affidavit facts essential to justify the party's opposition, the court may refuse the application for summary judgment or may order a continuance to permit affidavits to be obtained or discovery taken. Fed.R.Civ.P. 56(f).

VI. *The FDA's Demonstration*

The FDC Act provides that no new drug may be introduced into interstate commerce unless and until the FDA has approved an application for that drug. 21 U.S.C. §§ 355(a), 331(a). Before products such as FWC No. 1 and FWC No. 2 can be exempted from the statutory new drug preclearance procedures they must be "generally recognized" by qualified experts as safe and effective for their intended uses. 21 U.S.C. § 321(p). The "general recognition" requirement does not involve the actual safety or effectiveness of the product. Rather, it is the product's reputation in the scientific community that is relevant.

An expert's opinion as to general recognition must be based upon published well-controlled clinical studies meeting the requirements of 21 C.F.R. § 314.126 and may not be based on uncontrolled data and personal experience. Further, when a product contains more than one active ingredient, the contribution of each ingredient in the product must be scientifically demonstrated.

It is FDA's contention that there are no well-controlled clinical studies on the basis of which it can be concluded that FWC No. 1 and FWC No. 2 are effective for their labeled indications and there are none which show that each ingredient of the FWC products contributes to the effectiveness of these two products. This being so, FDA urges, it is entitled to summary judgment.

To establish the absence of a factual issue, the FDA has submitted the declaration of six highly qualified experts, William Forrest, M.D., Thomas Kantor, M.D.,

Michael Weintraub, M.D., Michael Lockshin, M.D., Richard Black, M.D. and Raymond Dionne, D.D.S., Ph.D. The FDA asked each of them to give his opinion regarding the general recognition of the safety and effectiveness of FWC No. 1 and FWC No. 2 and whether each component of the two drugs contributes to their effectiveness. Their factual statements and opinions were generally to the same effect. They can be summarized as follows:

The doctors described the contents of the two FWC products and referred to their labels which set forth the conditions for which the products may be used. They noted their familiarity with the requirements of 21 C.F.R. § 314.126 and 21 C.F.R. § 300.50.

As the manufacturer of a combination drug product Sandoz must show that each ingredient in FWC No. 1 and FWC No. 2 contributes to the claimed effects. Typical of the opinion of the six doctors is that of Dr. Forrest:

> 8.a. . . . To establish that FWC No. 1 complies with [§ 300.50 governing combination drug products], Sandoz must show that the addition of codeine (7.5 mg.) will significantly increase the effectiveness of the combination of aspirin (325 mg.), caffeine (40 mg.), and butalbital (50 mg.) to treat mild to moderate pain as indicated in this product's label. This must be done by conducting adequate and well-controlled studies in which the effect of the combination of aspirin, caffeine, and butalbital is compared *with* the effect of the combination of aspirin, caffeine, codeine, and butalbital (*i.e.*, FWC No. 1) in patients who have mild to moderate pain. The addition of 7.5 mg. codeine is justified only if there is significantly greater relief of pain in the latter group.
>
> b. Because FWC No. 1 also contains butalbital and caffeine, Sandoz must further show that the ad-

dition of each of these ingredients, *as formulated in FWC No. 1*, significantly increases the effectiveness of the FWC No. 1 combination. These showings must be made by comparing the pain relief achieved with FWC No. 1 against the relief achieved with additional control groups which eliminate each of the ingredients whose effect is to be measured (*e.g.*, to measure the contribution of butalbital, a group of patients must receive aspirin, caffeine and codeine; to measure the contribution of caffeine a group of patients must receive aspirin, codeine, and butalbital). (In my view, it is necessary to separately establish the contribution of caffeine in this product, even though there is reasonable evidence which shows that caffeine in larger doses (65 mg.) enhances the effectiveness of clinical doses of aspirin. I am not aware of any adequate and well-controlled studies which show that caffeine increases the effectiveness of aspirin when codeine and butalbital are present in the product.) The studies outlined in paragraphs 8a and 8b could be combined.

c. Because the foregoing reasoning applies with equal force to FWC No. 2, each of the showings described in paragraphs 8a and 8b above would have to be made with the FWC product which contains 15 mg. codeine phosphate.

The FDA doctors reviewed the published data which Sandoz furnished to the FDA and concluded that none of it contributes information on the safety and efficacy of FWC No. 1 and FWC No. 2 as they are presently constituted.

With respect to FWC No. 1, the experts noted that none of the studies analyzed an FWC product which contained 7.5 mg codeine phosphate. One of the studies reviewed by the FDA experts used the FWC No. 2 product which contained 15 mg codeine. The other studies reviewed by the FDA experts used FWC No. 3, a product

which contained 30 mg codeine. Thus the products which were studies contained two and four times the amount of codeine contained in FWC No. 1. There is, therefore, an absence of published clinical data to show that 7.5 mg codeine will contribute to the effects claimed for FWC No. 1.

Further, the FDA's experts found that the studies which Sandoz had submitted to the FDA contained deficiencies which rendered them not well-controlled and thus incapable of supporting the claims of either FWC No. 1 or FWC No. 2. The various clinical studies submitted in connection with this proceeding are described above. The FDA doctors addressed the three of them which Sandoz had submitted to the FDA during the course of its applications before that agency. They did not address three additional studies which Sandoz submitted in opposition to the summary judgment motion.

The FDA doctors referred first to the MacDonald and Ehrenreich study which compared the old FWC No. 2 formulation (containing phenacetin and only 200 mg aspirin) with APC with Codeine in an attempt, among other things, to establish the contribution of butalbital. The FDA doctors concluded that absent published data such as dissolution and/or bioavailability studies showing that removing phenacetin and increasing the aspirin did not affect the product, one cannot rely upon it as evidence that the butalbital contained in FWC No. 2 (as presently formulated) contributes to the effectiveness of the product.

The MacDonald and Ehrenreich study provides no data which would enable one to evaluate the contribution of caffeine in the product, nor was it designed to do so.

The FDA doctors noted certain defects in the MacDonald and Ehrenreich study, some of which were noted in the Forbes, et al. study upon which Sandoz relies. The study is flawed because the authors treated each episode of pain as a separate event even though the patients

could have received different drugs for each episode and many patients received multiple treatments, an approach that detracts from the reliability of the findings. Further, there was only one postoperation assessment and even that assessment was not made consistently at one hour.

The Madore and Chiricosta study merely compared one capsule of the old formulation of FWC No. 3 (containing phenacetin and 200 mg aspirin) with two capsules of old formulation FWC No. 3 with placebo. The FDA doctors concluded that this study is inapplicable to FWC No. 1 and FWC No. 2 because it studies a product containing phenacetin and 125 mg less aspirin and because it studied a product having four times as much codeine as FWC No. 1 and twice as much codeine as FWC No. 2. Furthermore there is nothing in the study which would enable a person to determine how much each component in the currently marketed FWC No. 1 and FWC No. 2 product contributes to the claimed effects.

The FDA doctors also critiqued the Friedman study which compared the effects of (i) the old formulation of FWC No. 3, (ii) the old formulation of plain Fiorinal, (iii) codeine (30 mg) and (iv) placebo.

This study rated only the contribution of codeine, containing no data concerning the contribution of butalbital or caffeine. The FDA experts stated that they could not take the butalbital data from MacDonald and apply it to the Friedman study. Apart from its various deficiencies and the fact that MacDonald studied old FWC No. 2 with 15 mg codeine and Friedman studied old FWC No. 3 with 30 mg codeine, in the MacDonald study the authors measured postoperative pain which, unlike tension headache measured by Friedman, is usually not described as having a tension component.

The FDA doctors found a number of general deficiencies in Friedman insofar as it purports to be a basis for conclusions about FWC No. 1 and FWC No. 2. It

examined FWC No. 3 which contains 30 mg codeine as compared to FWC No. 1's and FWC No. 2's codeine content of 7.5 mg and 15 mg, respectively. The study dealt with the old formulation of FWC No. 3 containing phenacetin and only 200 mg aspirin. The authors failed to provide data or analysis assuring that test and control groups were comparable with respect to pertinent variables such as age, sex, severity of disease or investigator effect. In any event, in view of the unusual separation of drug effects in so few patients, in the opinion of the FDA doctors there should be a replication in the same pain model.

One must conclude that the FDA has sustained its initial summary judgment burden. It has identified those portions of the record which it believes demonstrates the absence of a genuine issue of material fact. Its experts have identified what they consider to be the relevant published clinical studies. They have set forth what must be published in the way of clinical studies to establish the general recognition of FWC No. 1 and FWC No. 2 as safe and effective and what must be published to establish the contribution that each component of those products makes to their claimed effect. Finally they have made an initial showing that the requisite published clinical studies do not establish the requisite recognition of the product or contribution of its components.

The burden shifts to Sandoz to show a genuine issue of material fact.

VII. *Sandoz's Showing*

Sandoz asserts that there is an issue of material fact with respect to the new drug issue. To support its contention that there is evidence that published well-controlled clinical studies establish that the FWC products are generally recognized by qualified experts as safe and effective for their claimed uses and that each component contributes to their effectiveness, Sandoz has sub-

mitted three studies not referred to by the FDA experts and it has submitted the declarations of eight eminent medical doctors or scientists. The additional studies are those by Hwang, et al., Desjardins, et al. and Forbes, et al. The doctors and scientists are Donald J. Dalessio, M.D., Robert B. Daroff, M.D., Arnold P. Friedman, M.D., Victor Siegel, M.D., George W. Paulson, M.D., Irvin Warth, M.D., Dar-Shong Hwang, Ph.D., and Jack Singer, M.D. In addition Harry Baird, M.D., submitted a declaration reciting the history of FDA approval of Fiorinal (which originally contained aspirin 200 mg, phenacetin 132 mg, caffeine 40 mg, and butalbital 50 mg) and of the FDA's actions with respect to Fiorinal after issuance of the 1983 order for the removal of phenacetin. Further, Sandoz submitted the declaration of Karl A. Enright, M.D., who (under the name of K.A. Ehrenreich) conducted the study with MacDonald. He described certain of the procedures which were followed and attempted to answer the criticisms of the FDA experts.

I have reviewed with care the Sandoz submission. I conclude that Sandoz has produced evidence on the basis of which a rational trier of the facts could conclude that FWC No. 1 and FWC No. 2 are safe and effective for their intended uses and that each component contributes to the claimed benefits of the two products. However, I also conclude that even if the six studies relied upon by Sandoz are deemed to be well-controlled clinical studies, they do not establish general recognition by qualified experts that the particular drugs in this case and each of the components of those drugs are effective to produce the claimed results.

A. *The Evidence of Effectiveness and Contribution:* By means of the available studies, by means of many years experience using FWC products and by means of extrapolating data obtained from the studies and from other sources, Sandoz's experts were able to arrive at

their opinion that FWC products are in fact safe and effective for their intended uses and that each component contributes in one way or another to that effectiveness. It is significant that although there are three FWC products, only two of which are involved in this case, Sandoz's experts give global opinions about FWC products generally. They do not, and undoubtedly cannot on the basis of available data, differentiate between the three products when discussing their overall effect or the effect of their individual components. Because of the paucity of data they have had to treat as irrelevant the amount of codeine in each dosage.

The opinions of Sandoz's experts, which like the opinions of FDA's experts, are in good measure duplicative of each other, can be summarized as follows:

A single study evaluating each ingredient of FWC would be needlessly complex and a waste of resources. There are ample data, according to Sandoz's experts, in the published literature on FWC and that may be extrapolated to FWC from other published materials, and there is sufficient clinical experience of these experts to establish that FWC is more effective than each of its components and that each component contributes to the therapeutic effect.

The combination constituting FWC is a rational one. Aspirin, a peripherally acting agent, has well-recognized analgesic properties for all types of pain. Codeine, a centrally acting narcotic, has long been combined with aspirin and other peripheral analgesics. Where used together the additive effect is often substantially greater than would be achieved by administration of a higher degree of either aspirin or codeine alone. Caffeine has been shown to enhance the analgesic properties of aspirin and other analgesics. Butalbital is a barbituate having both sedative and muscle relaxing properties which are helpful in relieving the muscle contraction component of tension headache and muscular spasms that may be as-

sociated with other types of pain. Thus there is a general theoretical basis for concluding that FWC would be effective to relieve pain and that each constituent drug would contribute something to that effectiveness.

Sandoz's experts point to the six studies described to show that these generalized conclusions find support in adequate and well-controlled clinical trials. They acknowledge, as they must, that none of these studies tested FWC No. 1 and that only two of them tested FWC No. 2. They also acknowledge, as they must, that one of the two studies involving FWC No. 2 and three of the five studies testing FWC No. 3 tested the old formulation containing phenacetin (130 mg) and only 200 mg aspirin. Further, they acknowledge, as they must, that they rely on the MacDonald study to show that butalbital makes a contribution to the product and that there is no study involving FWC showing that caffeine makes a contribution. Nevertheless, the Sandoz experts conclude that by extrapolation from these studies as well as from other published data the necessary conclusions as to effectiveness and contribution can be made.

Conceding that Madore and Chiricosta was not designed to establish the contribution of any specific ingredient, the Sandoz experts state that it demonstrates the effectiveness of FWC versus placebo. They conclude that the 1983 formulation change involving the removal of phenacetin and increasing the aspirin dosage did not alter the effectiveness of the product and thus render less persuasive the Madore and Chiricosta study. The basis for this conclusion is that the FDA freely permitted substitution of aspirin or acetaminophen for phenacetin on a mg/mg basis. For example, Fiorinal, which had been approved by the FDA, was reformulated in this matter and the FDA did not require any new clinical trials. Confirmation of this conclusion was found in the Desjardins, et al. and Forbes, et al. studies which compared the present formulation of FWC No. 3 (Desjardins) and FWC No. 2

(Forbes) with placebo (and also with Tylenol with Codeine No. 3 and codeine alone in the case of Desjardins and also with Tylenol with Codeine No. 3 in the case of Forbes).

A greater degree of extrapolation and reliance on general knowledge and clinical experience is required by these experts in order to establish the contribution of each component of FWC.

Reliance is had on the MacDonald study to show the contribution of butalbital. In the Sandoz experts' opinion although the MacDonald study involved postsurgical pain the conclusion may be extrapolated to pain associated with muscle contraction. For reasons noted above although the MacDonald study involved the old formulation of FWC No. 2, it may be extrapolated to FWC No. 2 with the new formulation and to FWC No. 1.

To establish the effectiveness of codeine the Sandoz experts rely on "numerous articles concerning the enhanced effectiveness of analgesics with codeine" (Dalessio declaration p. 11) and upon the Friedman study, thus extrapolating the results of a study of the effect of codeine in a product having the old FWC No. 3 formulation and 30 mg codeine to new formulation FWC No. 2 having 15 mg codeine and to new formulation FWC No. 1 having 7.5 mg codeine. The Sandoz experts found the Hwang, et al. study to be confirmatory of the Friedman study.

None of the studies sought to evaluate the contribution of caffeine to any form of FWC. However, Sandoz's experts concluded that the fact of its contribution can be inferred on several bases. They refer to "available data concerning both caffeine and aspirin" which "may be extrapolated to support their contribution to Fiorinal with Codeine" (Siegel declaration p. 8). They refer to the fact that Fiorinal, which contains the same amounts of aspirin, caffeine and butalbital as FWC, was approved by the FDA, and therefore it must have been established

that caffeine made a contribution to the effect of Fiorinal. They suggest that the addition of codeine would not alter that effect.

Sandoz submitted an article which perhaps summarizes the "available data" concerning aspirin and caffeine to which its experts referred: Laska, E.M., et al., "Caffeine as an Analgesic Adjuvant", The Journal of the American Medical Association, Vol. 251, No. 13, Apr. 6, 1984. The article surveys 30 clinical studies conducted during the past 20 years in order to assess the value of caffeine as an analgesic adjuvant. It concluded that "[b]ased on these studies and a review of the literature, it seems reasonable to conclude that the addition of caffeine, 65 mg, to an analgesic tablet taken in a two-tablet dose results in a more effective analgesic." From this Sandoz's experts arrive at the opinion that the 40 mg caffeine in FWC would combine with the aspirin and result in a more effective product.

These are all rational conclusions. If FDA were contending that FWC No. 1 and FWC No. 2 were not in fact safe and effective and that each constituent drug does not contribute to the total effect of the product, then the evidence submitted by Sandoz would be more than sufficient to create a genuine issue of fact.

However, actual safety and effectiveness and actual contribution of the components to the total effect are not the issues, *e.g.*, *Premo Pharmaceutical Laboratories, Inc. v. United States*, 629 F.2d 795 (2d Cir. 1980). The issue is whether there is a lack of substantial evidence to support a finding that FWC No. 1 and FWC No. 2 are generally recognized as effective and a finding that each component of the two products contributes to their effectiveness, *e.g.*, *Weinberger v. Hynson, Westcott & Dunning, Inc.*, *supra*. Substantial evidence consists "of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training

and experience to evaluate the effectiveness of the drug involved. . . ." 21 U.S.C. § 355(d).

B. *The Lack of Substantial Evidence*: It is the FDA's position that the studies upon which Sandoz relies were not well-controlled clinical studies which meet the specific regulatory criteria. The FDA's experts pointed out what they considered to be deficiencies in the various studies. For the purposes of this opinion, however, I shall assume that they did meet the statutory and regulatory criteria. Their deficiency for the purpose of this case is that they did not adequately address the two drugs at issue and they did not adequately address the ingredients of those two drugs as used in those two drugs. The deficiencies cannot be remedied by the extensive clinical experience of Sandoz's experts who have prescribed some forms of FWC for a number of years. Nor can the deficiencies be remedied by the extensive extrapolation of data to which these experts resorted.

There is a rational bases for the requirement of 21 C.F.R. § 300.50 that in the case of a combination drug there be a showing that each active ingredient makes a contribution to the claimed effect. Most drugs are associated with some degree of risk. Further, any one component of a drug may react with or affect the safety and effectiveness of the other components of the drug. Accordingly, before two or more drugs may be combined into a single product, the manufacturer must demonstrate, by adequate and well-controlled investigations that each additional component provides a specific benefit to the patient that warrants the increased risk.

Sandoz's own evidence establishes that the clinical studies upon which it relies to establish the contribution of the components of FWC No. 1 and FWC No. 2 were not studies of either of those two drugs. Sandoz urges on a number of grounds that it should nevertheless prevail on this summary judgment motion.

Citing *Weinberger v. Bentex Pharmaceuticals, Inc.*, 412 U.S. 645, 93 S.Ct. 2488, 37 L.Ed.2d 235 (1973),

Sandoz contends that an exception to the well-controlled clinical investigations requirement exists for certain long-used drugs such as FWC No. 1 and FWC No. 2. In *Bentex* the Supreme Court stated that "[i]t *may* . . . be true" that "*in some cases*" general recognition "might" be made without the type of scientific data necessary to obtain approval by the FDA. 412 U.S. at 652, 93 S.Ct. at 2493. (Emphasis added). The Supreme Court did not refer to long-used drugs as being within such an exception, and subsequent case law does not disclose any specific category of cases which would fall within this dictum. The long use situation has specifically been held not to fall within any exception to the well-controlled clinical investigations requirement, *e.g., Upjohn Co. v. Finch*, 422 F.2d 944 (6th Cir.1970) (decided before *Bentex*); *United States v. Articles of Food and Drug . . . Coli-Trol 80 Medciated*, 372 F.Supp. 915 (N.D.Ga.1974) (decided after *Bentex*). Thus the extensive successful use of some forms of FWC by some of Sandoz's experts is not pertinent. Such use, of course, does not even purport to attest to the contribution of each FWC ingredient.

Sandoz contends that clinical studies of FWC containing phenacetin and 200 mg aspirin can be deemed to be clinical studies of FWC No. 1 and FWC No. 2 containing no phenacetin and 325 mg aspirin. Sandoz contends that inasmuch as FDA issued a Federal Register notice which required that phenacetin be removed from the old product and replaced with aspirin (or another analgesic), it must be concluded that the new and the old products will be equally efficacious. Force is given to this contention, Sandoz argues, by the fact that the FDA did not require new clinical trials of the newly formulated products.

It should be noted that the Federal Register notice was published under the authority of 21 U.S.C. § 355 governing *new drugs*. While the notice did not require manufacturers to conduct new clinical trials, it did require manufacturers to submit dissolution data and bio-

availability data to show that the reformulation did not affect the products. 47 Fed.Reg. at 36641, col. 2.

The significance of the data which the FDA called for is noted in Dr. Lockshin's declaration:

> The "new" and the "old" FWC No. 2 are simply two different products. They contain different amounts and types of active ingredients, and there is no published literature of which I am aware that establishes that these differences do not influence the effectiveness of the FWC No. 2 product. Such a showing could only be made by a direct comparison of the "new" and "old" FWC No. 2. Additionally, I am not aware of any published data which shows that the two products contain the identical inactive ingredients or were manufactured under precisely the same conditions. These factors are important because they may affect the bioequivalence of the two products (i.e., their comparative rate and extent of absorption of the active ingredients). The bioequivalence of the two FWC product [sic] can also properly be established only by direct comparison.

None of Sandoz's experts state that they have any knowledge of the inactive ingredients in the new or the old formulations and they do not mention bioequivalence. More to the point, Sandoz's experts do not refer to any well-controlled, published scientific data upon which experts can fairly conclude that each of the ingredients in the new and old formulations is bioequivalent.

Thus I conclude that studies conducted using the old formulation are not well-controlled clinical investigations of products using the new formulation and extrapolation of the data derived from them is not justified for the purpose of a "new drug" determination.

Sandoz advances a legal basis for applying clinical studies of contributions of components of FWC No. 3 (containing 30 mg codeine) to the ingredients of FWC

No. 2 (containing 15 mg codeine) and FWC No. 1 (containing 7.5 mg codeine). It advances the same legal basis for applying clinical studies of contributions of components of old formulations of FWC to ingredients of products containing the new formulations. It cites *United States v. An Article of Drug . . . Mykocert*, 345 F.Supp. 571 (N.D.Ill.1972) and *United States v. Entrol-C Medicated*, 513 F.2d 1127 (9th Cir.1975) for the proposition that the general recognition of a combination preparation could under certain circumstances be based upon the general recognition of its component parts, presumably as they manifested themselves in other contexts. I conclude that the proper rule and the rule that will be followed in this circuit is that the combination policy of 21 C.F.R. § 300.50 can only be met by studies of the particular drug product at issue or a drug having the same active ingredients which is demonstrably its bioequivalent. Even if *Mykocert* and *Entrol-C Medicated* were applied in this case, the exception to the general rule which they announce is limited and would not extend to the extrapolations Sandoz relies upon in this case.

Having made these general observations, I will state briefly the reasons why I have concluded that Sandoz has failed to produce evidence on the basis of which it could be found that published, well-controlled clinical studies establish recognition of the contribution of the ingredients of FWC No. 1 and FWC No. 2.

Initially, there has been no study of FWC No. 1 either with respect to its overall efficacy or with respect to its components.

There has been no study of any old or new FWC formulation to determine the contribution of 40 mg caffeine. Sandoz's experts described generally the phenomenon whereby combining caffeine with aspirin increases the effectiveness of aspirin. However, they did not specify what amount of caffeine was required or refer to any

data describing the effect of adding caffeine when butalbital and codeine were a part of the mixture. The 1984 Laska article described 30 studies (most of which were not published) none of which involved a product containing either butalbital or codeine. The Laska article concluded that the addition of *65* mg caffeine to an analgesic tablet taken in a two tablet dose results in a more effective analgesic. Thus there are no published, well-controlled clinical studies showing what contribution 40 mg caffeine makes or what contribution caffeine in any amount makes to FWC No. 1 and FWC No. 2.

The only published study purporting to show the contribution of butalbital is the 1966 MacDonald study using the old phenacetin-containing FWC No. 2. Apart from the various deficiencies in that study referred to by the FDA's experts and in the Forbes report submitted by Sandoz, the study was conducted on a product having a different formulation which has not been shown to be the bioequivalent of FWC No. 1 or FWC No. 2.

Even though Sandoz has submitted evidence on the basis of which one could conclude that in general codeine has pain-relieving qualities, it has not produced evidence of published, well-controlled clinical studies that codeine or the amount of codeine in FWC No. 1 (7.5 mg codeine) and FWC No. 2 (15 mg codeine) contribute to the effectiveness of the product.

The Friedman and the Hwang studies dealt with the old formulation of FWC No. 3 which contained twice as much codeine as FWC No. 2 and four times as much codeine as FWC No. 1. I am disregarding the deficiencies in those studies to which the FDA's experts referred.

The MacDonald study sought only to determine the contribution of butalbital. The Desjardins study dealt with FWC No. 3 and did not analyze the contribution of the components of the drugs studied. The Forbes study, which did deal with FWC No. 2, did not purport to assess

the effectiveness of each component. None of the Sandoz experts stated that either of the lower amounts of codeine in FWC No. 1 or FWC No. 2 make a clinically and statistically significant contribution to the seized articles, nor, more important, were there any published studies showing such contribution.

I conclude therefore that Sandoz has failed to produce evidence that there exist the published, well-controlled clinical studies on the basis of which one could find that FWC No. 1 and FWC No. 2 are generally recognized by qualified experts as effective for their intended use and that each of their active ingredients contributes to their effectiveness. FWC No. 1 and FWC No. 2 are, therefore, new drugs.

The only basis for denying the FDA's motion for summary judgment would be a showing by Sandoz that discovery would be likely to produce evidence which would preclude summary judgment. Sandoz has moved for a continuance and for leave to take discovery. I have noted the subjects about which Sandoz seeks to take discovery. Responses to the requested discovery could not fill the void in necessary published clinical investigations. The information sought appears to me to be irrelevant and consequently the motion for a continuance and for discovery will be denied.

VIII. *The Misbranding Claim*

Having found that FWC No. 1 and FWC No. 2 are new drugs, it follows that they are also misbranded within the meaning of 21 U.S.C. § 352(f)(1) and 21 C.F.R. § 201.100(c) because their labeling has not been approved by the FDA in the context of an NDA.

IX. *Remand for Administrative Review*

Sandoz asserts as an affirmative defense that the FDA has not made an administrative determination of

FWC's new drug status on the basis of an administrative record, and thus the matter should be remanded to the FDA for a formal administrative determination. This, Sandoz asserts, would assist the court in developing a factual record.

I see no reason to remand the case. An administrative proceeding is not mandated as a prerequisite to the institution of a seizure action under 21 U.S.C. § 334(a). The record before me is complete. There is nothing to suggest that there is any relevant published material which has not been submitted by one or the other of the parties. Remand would be at odds with the purposes of seizure, *Ewing v. Mytinger & Casselberry, Inc.*, 339 U.S. 594, 70 S.Ct. 870, 94 L.Ed. 1088 (1950); *United States v. Alcon Laboratories*, 636 F.2d 876 (1st Cir.), *cert. denied*, 451 U.S. 1017, 101 S.Ct. 3005, 69 L.Ed.2d 388 (1981).

Therefore, Sandoz's contention that the case should be remanded to the FDA is rejected.

X. *Conclusion*

Sandoz's motion for a continuance and for discovery will be denied. Sandoz's contention that the matter should be remanded to the FDA for administrative proceedings is rejected.

The FDA's motion for summary judgment on the new drug and misbranding issues is granted.

In its briefs in support of its motion for summary judgment the FDA asked for injunctive relief. Formal application for an injunction has not been made and consequently I will not act upon the request. The FDA may make formal application for an injunction if it wishes to do so.

The FDA is requested to submit a form of order implementing this opinion.

APPENDIX D

21 U.S.C.A. § 321(p) (West 1972):

(p) The term "new drug" means—

(1) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof, except that such a drug not so recognized shall not be deemed to be a "new drug" if at any time prior to the enactment of this chapter it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use; or

(2) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.

APPENDIX E

21 U.S.C.A. § 355(a) (West 1972):

(a) Necessity of effective approval of application

No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) of this section is effective with respect to such drug.

APPENDIX F

21 U.S.C.A. § 355(d) (West 1972):

(d) Grounds for refusing application; approval of application; "substantial evidence" defined

If the Secretary finds, after due notice to the applicant in accordance with subsection (c) of this section and giving him an opportunity for a hearing, in accordance with said subsection, that (1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b) of this section, do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof; (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; (3) the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity; (4) upon the basis of the information submitted to him as part of the application, or upon the basis of any other information before him with respect to such drug, he has insufficient information to determine whether such drug is safe for use under such conditions; or (5) evaluated on the basis of the information submitted to him as part of the application and any other information before him with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof; or (6) the application failed to contain the patent information prescribed by subsection (b) of this section; or (7) based on a fair evaluation of all material facts, such labeling is false or misleading in any particular; he shall issue an order re-

fusing to approve the application. If, after such notice and opportunity for hearing, the Secretary finds that clauses (1) through (6) do not apply, he shall issue an order approving the application. As used in this subsection and subsection (e) of this section, the term "substantial evidence" means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

APPENDIX G

21 C.F.R. § 300.50 (1989):

§ 300.50 Fixed-combination prescription drugs for humans.

The Food and Drug Administration's policy in administering the new-drug, antibiotic, and other regulatory provisions of the Federal Food, Drug, and Cosmetic Act regarding fixed combination dosage form prescription drugs for humans is as follows:

(a) Two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug. Special cases of this general rule are where a component is added:

(1) To enhance the safety or effectiveness of the principal active component; and

(2) To minimize the potential for abuse of the principal active component.

(b) If a combination drug presently the subject of an approved new-drug application or antibiotic monograph has not been recognized as effective by the Commissioner of Food and Drugs based on his evaluation of the appropriate National Academy of Sciences-National Research Council panel report, or if substantial evidence of effectiveness has not otherwise been presented for it, then formulation, labeling, or dosage changes may be proposed and any resulting formulation may meet the appropriate criteria listed in paragraph (a) of this section.

(c) A fixed-combination prescription drug for humans that has been determined to be effective for labeled indi-

cations by the Food and Drug Administration, based on evaluation of the NAS-NRC report on the combination, is considered to be in compliance with the requirements of this section.